30 mg total amphetamine (as 7.5 mg, with Amphetamine Aspartate 7.5 mg, Dextroamphetamine Saccharate 7.5 mg, and Dextroamphetamine Sulfate 7.5 mg)*	**Adderall** (C-II; double-scored), Shire
	Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Dextroamphetamine

■ Dextroamphetamine is the dextrorotatory isomer of amphetamine.

Uses

Dextroamphetamine sulfate alone and in fixed-combination preparations with dextroamphetamine saccharate, amphetamine aspartate, and amphetamine sulfate is used in the treatment of narcolepsy and as an adjunct to psychological, educational, social, and other remedial measures in the treatment of attention deficit hyperactivity disorder (ADHD).

■ Narcolepsy and Attention Deficit Hyperactivity Disorder

Dextroamphetamine sulfate alone and in fixed-combination preparations with dextroamphetamine saccharate, amphetamine aspartate, and amphetamine sulfate is used in the treatment of narcolepsy and as an adjunct to psychological, educational, social, and other remedial measures in the treatment of ADHD (hyperkinetic disorder, hyperkinetic syndrome of childhood, minimal brain dysfunction) in children, adolescents, and adults.

ADHD usually is characterized by developmentally inappropriate symptoms (e.g., moderate to severe distractibility, short attention span, hyperactivity, emotional lability, impulsivity). The final diagnosis of this disorder should not be made if these symptoms are of only comparatively recent origin. Nonlocalizing (soft) neurologic signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of CNS dysfunction may or may not be warranted. Drug therapy is not indicated in all children with ADHD, and such therapy should be considered only after a complete evaluation including medical history has been performed. The decision to use amphetamines should depend on the age of the child and the clinician's assessment of the severity and duration of symptoms and should not depend solely on one or more behavioral characteristics. When symptoms of ADHD are associated with acute stress reactions, use of amphetamines usually is not recommended. For a more detailed discussion on the management of ADHD, including the use of stimulants such as dextroamphetamine, see Uses: Attention Deficit Hyperactivity Disorder, in Methylphenidate 28:20.92.

Dosage and Administration

■ Administration

Preparations containing dextroamphetamine sulfate are administered orally. The commercially available extended-release capsules containing dextroamphetamine sulfate and dextroamphetamine saccharate in fixed-combination with amphetamine sulfate and amphetamine aspartate (Adderall XR®) may be swallowed intact with or without food or the entire contents of a capsule(s) may be sprinkled on a small amount of applesauce immediately prior to administration; subdividing the contents of a capsule is not recommended. The pellets contained in the capsules should not be chewed or crushed, and the sprinkle/food mixture must not be stored for use at a later time.

The initial dose of dextroamphetamine sulfate (alone or in fixed-combination preparations) is given on awakening; when the drug is given as conventional (short-acting) tablets in divided doses (2 or 3), additional doses are given at intervals of 4–6 hours. Because of the potential for insomnia, administration of dextroamphetamine sulfate conventional tablets (Dexedrine®), dextroamphetamine sulfate extended-release capsules (Dexedrine® Spansules®), or fixed-combination conventional tablets (Adderall®) in the late evening or administration of fixed-combination extended-release capsules (Adderall XR®) in the afternoon should be avoided.

■ Dosage

Dosage of dextroamphetamines should be adjusted according to individual response and tolerance; the smallest dose required to produce the desired response should always be used.

Narcolepsy In the treatment of narcolepsy, the usual dosage of dextroamphetamine sulfate given alone or the total dosage of amphetamines given in fixed-combination preparations containing dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate, and amphetamine sulfate is 5–60 mg daily, depending upon the patient's age and response, usually given in divided doses. In patients 12 years of age and older, the initial dosage is 10 mg daily; daily dosage is increased by 10 mg at weekly intervals until the optimum response is attained. Although narcolepsy seldom occurs in children younger than 12 years of age, in pediatric patients 6–12 years of age, the recommended initial dosage of dextroamphetamine sulfate is 5 mg daily; daily dosage is increased by 5 mg at weekly intervals until the optimum response is attained. When intolerable adverse effects occur (e.g., insomnia, anorexia), dosage should be reduced. Dextroamphetamine sulfate extended-release capsules may be used for once-daily dosing whenever appropriate.

Attention Deficit Hyperactivity Disorder Dextroamphetamine sulfate dosage for the treatment of attention deficit hyperactivity disorder (ADHD) should be individualized based on patient response and tolerance. The first dosage that produces an observable response may not be the optimum dosage to improve function, and titration to higher dosages should continue in an attempt to achieve a better response. Such a strategy may require subsequent lowering of dosage when higher dosages produce adverse effects or no further clinical improvement. The best dosage for a given patient is the one that provides optimum therapeutic effects with minimal adverse effects. Dosing schedules also may vary, although there currently are no consistent controlled studies comparing alternative dosing schedules. Patients who require relief only during school may respond adequately to a 5-day (i.e., school day) regimen while those requiring relief at home and school may need a daily regimen throughout the week.

As an adjunct in the treatment of ADHD in children 6 years of age and older, the initial dosage of dextroamphetamine sulfate given in conventional (short-acting) preparations is 5 mg once or twice daily; daily dosage is increased by 5 mg at weekly intervals until the optimum response is attained. The usual dosage range is 5–15 mg twice daily or 5–10 mg 3 times daily. Total daily dosage rarely should exceed 40 mg. In children 3–5 years of age, the initial daily dosage is 2.5 mg; daily dosage is increased by 2.5 mg at weekly intervals until the optimum response is attained. When the drug is administered as conventional tablets in divided doses (2 or 3), additional doses are given at intervals of 4–6 hours. Dextroamphetamine sulfate extended-release capsules can be substituted for their respective conventional short-acting preparations if less frequent daily dosing is desirable.

Dextroamphetamine sulfate in fixed combination with other amphetamines (dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate, and amphetamine sulfate) also is used as an adjunct in the treatment of ADHD in children 6 years of age and older; the initial total dosage of amphetamines is 5 mg once or twice daily. The daily dosage is increased by 5 mg at weekly intervals until the optimum response is attained; total daily dosage rarely should exceed 40 mg. In children 3–5 years of age, the initial daily dosage is 2.5 mg; daily dosage is increased by 2.5 mg at weekly intervals until the optimum response is attained. The manufacturer recommends that the initial dose of dextroamphetamine sulfate in fixed combination with other amphetamines be given on awakening; additional doses (1 or 2) are given at intervals of 4–6 hours. The usual dosage for intermediate-acting preparations (e.g., Dexedrine® Spansules®, Adderall®) in children 6 years of age and older is 5–30 mg once daily or 5–15 mg twice daily.

Alternatively, in patients who are receiving drug therapy for ADHD for the first time or are being switched from therapy with another stimulant, dextroamphetamine therapy may be initiated with extended-release capsules containing dextroamphetamine sulfate in fixed-combination with dextroamphetamine saccharate, amphetamine aspartate, and amphetamine sulfate (Adderall XR®). In children 6–12 years of age, the initial dosage of total amphetamines as fixed-combination extended-release capsules (Adderall XR®) is 10 mg once daily; daily dosage may be increased in increments of 5 or 10 mg at weekly intervals to a maximum dosage of 30 mg daily. Treatment may be initiated with a dosage of 5 mg once daily when, in the opinion of the clinician, a lower initial dosage is appropriate. The usual dosage for such longer-acting preparations (e.g., Adderall XR®) is 10–30 mg daily. In adolescents 13–17 years of age, the initial dosage of total amphetamines as fixed-combination extended-release capsules (Adderall XR®) is 10 mg once daily. Dosage may be increased to 20 mg once daily after 1 week if symptoms are not adequately controlled. In adults who are receiving drug therapy for ADHD for the first time or are being switched from therapy with another drug, the recommended dosage of amphetamines as fixed-combination extended-release capsules (Adderall XR®) is 20 mg once daily. Although dosages of up to 60 mg daily (as fixed-combination extended-release capsules) have been used in adolescents 13–17 years of age and adults in clinical studies, there is no evidence that dosages exceeding 20 mg daily provide any additional benefit in these patients. When switching from fixed-combination conventional tablets (Adderall®) to fixed-combination extended-release capsules (Adderall XR®), the total daily dosage of amphetamines may remain the same but should be given once daily.

When possible, therapy should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued treatment. Long-term use of fixed-combination extended-release capsules (i.e., more than 3 weeks in children or more than 4 weeks in adolescents or adults) has not been studied systematically. If fixed-combination extended-release capsules are used for extended periods, the usefulness of the drug should be periodically reevaluated.

Cautions

Dextroamphetamine shares the toxic potentials of amphetamines, and the usual cautions, precautions, and contraindications of amphetamine therapy should be observed. (See Cautions in the Amphetamines General Statement 28:20.04.)

Some commercially available preparations of dextroamphetamine (e.g., DextroStat®, Dexedrine® tablets) contain the dye tartrazine (FD&C yellow No. 5), which may cause allergic reactions including bronchial asthma in susceptible individuals. Although the incidence of tartrazine sensitivity is low, it frequently occurs in patients who are sensitive to aspirin.

Chemistry and Stability

■ **Chemistry** Dextroamphetamine is the dextrorotatory isomer of amphetamine. Dextroamphetamine sulfate occurs as a white, odorless, crystalline powder and has a bitter taste. Dextroamphetamine sulfate is freely soluble in water (about 1:10) and slightly soluble in alcohol (about 1:800). Dextroamphetamine sulfate also is commercially available as fixed-combination preparations with dextroamphetamine saccharate, amphetamine aspartate, and amphetamine sulfate.

■ **Stability** Preparations containing dextroamphetamine sulfate should be stored in tight, light-resistant containers at 15–30°C.

Preparations

Dextroamphetamine and dextroamphetamine sulfate preparations are subject to control under the Federal Controlled Substances Act of 1970 as schedule II (C-II) drugs.

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Dextroamphetamine Sulfate

Oral

Capsules, extended-release	5 mg*	**Dexedrine® Spansule®** (C-II), GlaxoSmithKline
		Dextroamphetamine Sulfate Capsules SR (C-II)
	10 mg*	**Dexedrine® Spansule®** (C-II), GlaxoSmithKline
		Dextroamphetamine Sulfate Capsules SR (C-II)
	15 mg*	**Dexedrine® Spansule®** (C-II), GlaxoSmithKline
		Dextroamphetamine Sulfate Capsules SR (C-II)
Tablets	5 mg*	**Dexedrine®** (C-II; scored), GlaxoSmithKline
		Dextroamphetamine Sulfate Tablets (C-II; scored)
		DextroStat® (C-II; scored), Shire
	10 mg*	**Dextroamphetamine Sulfate Tablets** (C-II; scored)
		DextroStat® (C-II; double-scored), Shire

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Dextroamphetamine Sulfate Combinations

Oral

Capsules, extended-release	5 mg total amphetamine (as 1.25 mg with Amphetamine Sulfate 1.25 mg, Amphetamine Aspartate 1.25 mg, and Dextroamphetamine Saccharate 1.25 mg)	**Adderall XR®** (C-II), Shire
	10 mg total amphetamine (as 2.5 mg with Amphetamine Sulfate 2.5 mg, Amphetamine Aspartate 2.5 mg, and Dextroamphetamine Saccharate 2.5 mg)	**Adderall XR®** (C-II), Shire
	15 mg total amphetamine (as 3.75 mg with Amphetamine Sulfate 3.75 mg, Amphetamine Aspartate 3.75 mg, and Dextroamphetamine Saccharate 3.75 mg)	**Adderall XR®** (C-II), Shire
	20 mg total amphetamine (as 5 mg with Amphetamine Sulfate 5 mg, Amphetamine Aspartate 5 mg, and Dextroamphetamine Saccharate 5 mg)	**Adderall XR®** (C-II), Shire
	25 mg total amphetamine (as 6.25 mg with Amphetamine Sulfate 6.25 mg, Amphetamine Aspartate 6.25 mg, and Dextroamphetamine Saccharate 6.25 mg)	**Adderall XR®** (C-II), Shire
	30 mg total amphetamine (as 7.5 mg with Amphetamine Sulfate 7.5 mg, Amphetamine Aspartate 7.5 mg, and Dextroamphetamine Saccharate 7.5 mg)	**Adderall XR®** (C-II), Shire
Tablets	5 mg total amphetamine (as 1.25 mg with Amphetamine Aspartate 1.25 mg, Amphetamine Sulfate 1.25 mg, and Dextroamphetamine Saccharate 1.25 mg)*	**Adderall®** (C-II; double-scored), Shire
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)
	7.5 mg total amphetamine (as 1.875 mg with Amphetamine Aspartate 1.875 mg, Amphetamine Sulfate 1.875 mg, and Dextroamphetamine Saccharate 1.875 mg)*	**Adderall®** (C-II; double-scored), Shire
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)
	10 mg total amphetamine (as 2.5 mg with Amphetamine Aspartate 2.5 mg, Amphetamine Sulfate 2.5 mg, and Dextroamphetamine Saccharate 2.5 mg)*	**Adderall®** (C-II; double-scored), Shire
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)
	12.5 mg total amphetamine (as 3.125 mg with Amphetamine Aspartate 3.125 mg, Amphetamine Sulfate 3.125 mg, and Dextroamphetamine Saccharate 3.125 mg)*	**Adderall®** (C-II; double-scored), Shire
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)
	15 mg total amphetamine (as 3.75 mg with Amphetamine Aspartate 3.75 mg, Amphetamine Sulfate 3.75 mg, and Dextroamphetamine Saccharate 3.75 mg)*	**Adderall®** (C-II; double-scored), Shire
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)
	20 mg total amphetamine (as 5 mg with Amphetamine Aspartate 5 mg, Amphetamine Sulfate 5 mg, and Dextroamphetamine Saccharate 5 mg)*	**Adderall®** (C-II; double-scored), Shire
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)
	30 mg total amphetamine (as 7.5 mg with Amphetamine Aspartate 7.5 mg, Amphetamine Sulfate 7.5 mg, and Dextroamphetamine Saccharate 7.5 mg)*	**Adderall®** (C-II; double-scored), Shire
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate and Amphetamine Sulfate Tablets (C-II; double-scored)

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Lisdexamfetamine Dimesylate

■ Prodrug of dextroamphetamine; noncatechol, sympathomimetic amine with CNS-stimulating activity.

Uses

■ **Attention-Deficit Hyperactivity Disorder** Lisdexamfetamine dimesylate is used as an adjunct to psychological, educational, social, and other remedial measures in the treatment of attention deficit hyperactivity disorder (ADHD) (hyperkinetic disorder, hyperkinetic syndrome of childhood, minimal brain dysfunction). Safety and efficacy for this indication have been established in controlled clinical trials in children 6–12 years of age and in adults.

Safety and efficacy of lisdexamfetamine dimesylate in the treatment of ADHD in children 6–12 years of age who met DSM-IV-TR criteria for ADHD (combined type or predominantly hyperactive-impulsive type) have been evaluated in 2 randomized, double-blind, placebo-controlled clinical studies (one phase 2 and one phase 3). The phase 2 crossover study was conducted in an analog classroom environment. In this study, dosage of amphetamines was titrated over a 3-week period using an extended-release formulation of mixed amphetamine salts (Adderall XR®) to a final dosage of 10, 20, or 30 mg daily; the children then were assigned to receive, in randomly determined sequence, 1 week each of treatment with extended-release mixed amphetamine salts (continued at the same dosage), lisdexamfetamine dimesylate (30, 50, or 70 mg

■ **CNS-active Drugs** Potential pharmacologic interaction when given with or substituted for other centrally acting drugs, including those with a similar mechanism of action; use with caution.

■ **5-HT$_1$ Receptor Agonists ("Triptans")** Pharmacologic interaction (potentially life-threatening serotonin syndrome) if used concurrently with 5-HT$_1$ receptor agonists (e.g., almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan). If concomitant use is clinically warranted, the patient should be observed carefully, particularly during treatment initiation, when dosage is increased, or when another serotonergic agent is initiated. (See Serotonin Syndrome under Warnings/Precautions:Other Warnings and Precautions, in Cautions.)

■ **Monoamine Oxidase (MAO) Inhibitors** Pharmacologic interaction (potentially fatal serotonin syndrome); concomitant use is contraindicated. The manufacturer recommends that at least 2 weeks should elapse between discontinuance of an MAO inhibitor and initiation of duloxetine and that at least 5 days elapse between discontinuance of duloxetine therapy and initiation of MAO inhibitor therapy. (See Serotonin Syndrome under Warnings/Precautions:Other Warnings and Precautions, in Cautions.)

■ **Selective Serotonin-reuptake Inhibitors and Selective Serotonin- and Norepinephrine-reuptake Inhibitors** Potential pharmacologic interaction (potentially life-threatening serotonin syndrome); concurrent administration not recommended. (See Serotonin Syndrome under Warnings/Precautions:Other Warnings and Precautions, in Cautions.)

Concomitant administration of duloxetine and fluvoxamine, a potent CYP1A2 inhibitor, in poor CYP2D6 metabolizers resulted in a six-fold increase in duloxetine AUCs and peak plasma concentrations.

■ **Serotonergic Drugs** Potential pharmacologic interaction (potentially life-threatening serotonin syndrome) with drugs affecting serotonergic neurotransmission, including linezolid (an anti-infective agent that is a nonselective, reversible MAO inhibitor), lithium, tramadol, and St. John's wort *(Hypericum perforatum)*; use with caution. Concurrent administration of serotonin precursors (such as tryptophan) is not recommended. (See Serotonin Syndrome under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

■ **Smoking** Potential pharmacokinetic interaction (reduced duloxetine bioavailability and plasma concentrations). The manufacturer states that routine dosage adjustment is not necessary. However, some clinicians recommend a small increase in duloxetine dosage (about 15%) in patients who smoke.

■ **Theophylline** Although small increases (averaging from 7–20%) in theophylline AUCs have been reported during concurrent administration of theophylline and duloxetine; combined use of these drugs reportedly has been well tolerated and routine theophylline dosage adjustment does not appear to be necessary during concomitant administration.

■ **Thioridazine** Potential pharmacokinetic (increased plasma thioridazine concentrations) interaction with resulting increased risk of serious ventricular arrhythmias and sudden death; concomitant use is not recommended by manufacturer of duloxetine.

Description

Duloxetine hydrochloride, a selective serotonin- and norepinephrine-reuptake inhibitor (SNRI), is an antidepressant and anxiolytic agent. The drug also has demonstrated analgesic activity in animal models of chronic and persistent pain and in clinical trials evaluating the drug's activity in conditions associated with chronic pain (e.g., neuropathic pain, fibromyalgia). Duloxetine hydrochloride is pharmacologically related to venlafaxine hydrochloride and desvenlafaxine succinate.

The exact mechanisms of the antidepressant, anxiolytic, and central pain inhibitory actions of duloxetine have not been fully elucidated, but appear to be associated with the drug's potentiation of serotonergic and norudrenergic activity in the CNS. Like venlafaxine and desvenlafaxine, duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. Duloxetine does not inhibit monoamine oxidase (MAO) and has not demonstrated significant affinity for dopaminergic, adrenergic, cholinergic, γ-aminobutyric acid (GABA), glutamate, histaminergic, and opiate receptors in vitro.

Although the precise mechanism of action of duloxetine in stress urinary incontinence is unknown, it is thought to be related to potentiation of serotonin and norepinephrine activity in the sacral spinal cord, which increases urethral closure forces and thereby reduces involuntary urine loss.

Duloxetine is extensively metabolized in the liver, principally via oxidation by the cytochrome P-450 (CYP) 2D6 and 1A2 isoenzymes. Duloxetine is a moderate inhibitor of CYP2D6 and a somewhat weak inhibitor of CYP1A2. The drug is not an inhibitor of CYP2C9, CYP2C19, or CYP3A, nor is it an inducer of CYP1A2 or CYP3A.

Advice to Patients

Risk of suicidality; importance of patients, family, and caregivers being alert to and immediately reporting emergence of suicidality, worsening depression, or unusual changes in behavior, especially during the first few months of therapy or during periods of dosage adjustment. FDA recommends providing written patient information (medication guide) explaining risks of suicidality each time the drug is dispensed.

Importance of promptly reporting any manifestations of liver dysfunction (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness, unexplained flu-like symptoms) to clinician.

Importance of informing patient of risk of severe liver injury associated with concomitant use of duloxetine and heavy alcohol intake. (See Hepatic Effects under Warnings/Precautions: Other Warnings and Precautions and also see Drug Interactions: Alcohol.)

Risk of psychomotor impairment; importance of exercising caution while operating hazardous machinery, including automobile driving, until patient gains experience with the drug's effects.

Importance of advising patients of risk of orthostatic hypotension and syncope, particularly during initial therapy and subsequent dosage escalation and during concomitant therapy with drugs that may potentiate the orthostatic effect of duloxetine.

Importance of informing patients of risk of serotonin syndrome with concurrent use of duloxetine and 5-HT$_1$ receptor agonists (also called triptans), tramadol, or other serotonergic agents. Importance of seeking immediate medical attention if symptoms of serotonin syndrome develop.

Importance of taking medication exactly as prescribed by the clinician. Importance of informing patients that the delayed-release capsules should be swallowed whole and should not be chewed or crushed, nor should the capsule contents be sprinkled on food or mixed with liquids.

Importance of continuing duloxetine therapy even if a response is not evident within 1–4 weeks, unless directed otherwise.

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, as well as any concomitant illnesses (e.g., bipolar disorder, liver disease) or family history of suicidality or bipolar disorder. Risk of bleeding associated with concomitant use of duloxetine with aspirin or other nonsteroidal anti-inflammatory agents, warfarin, or other drugs that affect coagulation.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview[a] (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Duloxetine Hydrochloride

Oral		
Capsules, delayed-release (containing enteric-coated pellets)	20 mg (of duloxetine)	**Cymbalta®, Lilly**
	30 mg (of duloxetine)	**Cymbalta®, Lilly**
	60 mg (of duloxetine)	**Cymbalta®, Lilly**

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Venlafaxine Hydrochloride

■ Venlafaxine hydrochloride, a selective serotonin- and norepinephrine-reuptake inhibitor (SNRI), is a phenylethylamine-derivative antidepressant and anxiolytic agent.

Uses

■ **Major Depressive Disorder** Venlafaxine hydrochloride is used in the treatment of major depressive disorder. Efficacy of venlafaxine conventional tablets for the management of major depression has been established in several placebo-controlled studies in outpatient settings in patients who had major depression and in 1 placebo-controlled study in a hospital setting in patients who had major depression with melancholia. Efficacy of venlafaxine extended-release capsules for the treatment of major depression also has been established by controlled studies of 8–12 weeks' duration in outpatient settings; however, the safety and efficacy of venlafaxine extended-release capsules in hospitalized patients with major depression have not been adequately evaluated.

In 4 studies of 6 weeks' duration in adult outpatients with major depression, venlafaxine in dosages of 75–225 mg daily administered in 2 or 3 divided doses as conventional tablets was found to be superior to placebo on at least 2 of the following 3 clinical measures of depression: Hamilton Depression Rating Scale (HAM-D) total score, HAM-D depressed mood item, and the Clinical Global

Impression (CGI) Severity of Illness Scale. In these studies, higher dosages (i.e., dosages exceeding 225 mg daily) were not associated with greater response. In 2 short-term (8 or 12 weeks), placebo-controlled, flexible-dose (75–225 mg daily) studies with venlafaxine extended-release capsules in adult outpatients, venlafaxine was found to be superior to placebo on the same clinical measures of depression that were used in the studies of venlafaxine conventional tablets, as well as on the Montgomery-Asberg Depression Rating Scale (MADRS) total score and certain factors of the HAM-D, including the anxiety/somatization factor, the cognitive disturbance factor, the retardation factor, and the psychic anxiety score.

Venlafaxine also has been shown to be superior to placebo in the management of major depression with melancholia in a hospital setting. In a study of 4 weeks' duration, 65% of hospitalized patients with major depressive disorder and melancholia who received venlafaxine 150–375 mg daily (mean dosage of 350 mg daily) administered in 3 divided doses as conventional tablets had at least a 50% reduction in MADRS total score compared with 28% of those who received placebo. Patients who participated in this study had a mean baseline MADRS total score of 35 (range: 26–48); those with a baseline score of 4 or greater on the suicidal thought item of the MADRS were excluded from the study.

Results of long-term, relapse prevention studies in outpatients with major depression indicate that venlafaxine's antidepressant effects are maintained for up to 1 year. In these studies, patients who responded to an initial 8-week course of venlafaxine 75–225 mg once daily (as extended-release capsules) or an initial 26-week course of venlafaxine 100–200 mg daily in 2 divided doses (as conventional tablets) were randomized to receive either venlafaxine (same dosage range) or placebo. Patients receiving venlafaxine experienced substantially lower relapse rates than those receiving placebo. Relapse was defined in clinical studies with venlafaxine conventional tablets as a score of 4 or greater on the CGI Severity of Illness Scale and in clinical studies with venlafaxine extended-release capsules as a reappearance of major depressive disorder as defined by DSM-IV criteria and a CGI Severity of Illness score of 4 or greater (i.e., moderately severe depression), 2 consecutive scores of 4 or greater on the CGI Severity of Illness Scale, or a final CGI Severity of Illness score of 4 or greater for any patient who withdrew from the study for any reason.

For further information on treatment of major depressive disorder and considerations in choosing the most appropriate antidepressant for a particular patient, including considerations related to patient tolerance, patient age, and cardiovascular, sedative, and suicidal risk, see Considerations in Choosing Antidepressants under Uses: Major Depressive Disorder, in Fluoxetine Hydrochloride 28:16.04.20.

■ **Generalized Anxiety Disorder** Venlafaxine hydrochloride is used in the treatment of generalized anxiety disorder. Efficacy of venlafaxine extended-release capsules for the management of generalized anxiety disorder has been established in 4 randomized, multicenter, placebo-controlled studies of 2 or 6 months' duration in adult outpatients who met DSM-IV criteria for generalized anxiety disorder. Three studies employed fixed venlafaxine dosages, and the other employed a flexible dosing schedule. In the flexible-dose study, approximately 69% of patients receiving venlafaxine (75–225 mg daily as extended-release capsules) were categorized as responders (defined as a 40% or greater reduction from baseline in the Hamilton Rating Scale for Anxiety [HAM-A] total score or a score of 1 ["very much improved"] or 2 ["much improved"] on the Clinical Global Impressions [CGI] Global Improvement Scale) during weeks 6–28 of therapy compared with 42–46% of those receiving placebo. In separate clinical studies of 2 or 6 months' duration employing fixed dosages of venlafaxine (37.5, 75, 150, or 225 mg daily as extended-release capsules), venlafaxine was shown to be substantially more effective than placebo on HAM-A total score, both the HAM-A anxiety and tension items, and the CGI Scale. While a relationship between dosage (over the dosage range of 75–225 mg daily) and efficacy in generalized anxiety disorder has not been definitively established, dosages of 37.5 mg daily were not as consistently effective in one study as dosages of 75 or 150 mg daily.

■ **Social Phobia** Venlafaxine hydrochloride is used in the treatment of social phobia (social anxiety disorder). Efficacy of venlafaxine extended-release capsules in the treatment of social phobia has been established in 2 multicenter, placebo-controlled studies of 12 weeks' duration in adult outpatients who met DSM-IV criteria for social phobia. In these studies, venlafaxine (75–225 mg daily administered as extended-release capsules) was substantially more effective than placebo, as determined by change from baseline in the Liebowitz Social Anxiety Scale (LSAS) total score.

Subgroup analysis of these controlled studies in adult outpatients with social anxiety disorder did not reveal any evidence of gender-related differences in treatment outcome; there was insufficient information to determine the effect of age or race on outcome in these studies.

■ **Panic Disorder** Venlafaxine hydrochloride is used in the treatment of panic disorder with or without agoraphobia. Efficacy of venlafaxine extended-release capsules in the treatment of panic disorder has mainly been established in 2 multicenter, double-blind, placebo-controlled studies of 12 weeks' duration in adult outpatients who met DSM-IV criteria for panic disorder with or without agoraphobia. Venlafaxine was given in a fixed dosage of 75 or 150 mg once daily as extended-release capsules in one study and in a fixed dosage of 75 or 225 mg once daily as extended-release capsules in the other study. Venlafaxine was found to be substantially more effective than placebo, as determined by percentage of patients free of full-symptom attacks on the Panic and Anticipatory Anxiety Scale (PAAS), mean change from baseline on the Panic Disorder Severity Scale (PDSS) total score, and the percentage of patients rated as responders on the Clinical Global Impressions (CGI) Improvement Scale. While a relationship between dosage (over the dosage range of 75–225 mg daily) and efficacy in panic disorder has not been definitively established, efficacy was established for each dosage studied in these 2 trials.

Subgroup analysis of these controlled studies in adult outpatients with panic disorder did not reveal any evidence of gender-related differences in treatment outcome; there was insufficient information to determine the effect of age or race on outcome in these studies.

In a longer-term study, patients meeting DSM-IV criteria for panic disorder who had responded during the 12-week open phase of a clinical trial with venlafaxine (75, 150, or 225 mg once daily as extended-release capsules) were randomly assigned to either continue receiving venlafaxine in the same dosage range or be switched to placebo and observed for relapse. Relapse was defined as having 2 or more full-symptom panic attacks per week for 2 consecutive weeks or having discontinued therapy due to loss of effectiveness as determined by the study investigators. Patients who continued receiving venlafaxine therapy experienced a significantly longer time to relapse than those receiving placebo in this study.

■ **Vasomotor Symptoms** Venlafaxine has been used for the management of vasomotor symptoms† in women with breast cancer and in postmenopausal women. Therapy with the drug has improved both the frequency and severity of vasomotor symptoms (hot flushes [flushes]) in these women.

Most women receiving systemic antineoplastic therapy for breast cancer experience vasomotor symptoms, particularly those receiving tamoxifen therapy. In a randomized, double-blind, placebo-controlled study in 191 women with breast cancer (69% were receiving tamoxifen) who were experiencing 2 or more episodes of hot flushes daily, the percentage reductions in hot flush severity score at 4 weeks of treatment were 27% for placebo, 37% for venlafaxine 37.5 mg daily, 61% for venlafaxine 75 mg daily, and 61% for venlafaxine 150 mg daily. Comparisons among treatment groups showed that all 3 venlafaxine dosages were associated with a statistically significant reduction in hot flush frequency and severity; in addition, the 75-mg dosage was more effective than the 37.5-mg dosage, but the 150-mg dosage provided no additional benefit. The role of venlafaxine in managing vasomotor symptoms in women with breast cancer relative to other nonhormonal therapies (e.g., selective serotonin-reuptake inhibitors [SSRIs], gabapentin) remains to be determined. Well-designed, comparative studies are needed to establish optimum nonhormonal therapy, both in terms of efficacy and patient tolerance of adverse effects in these women.

Because of the risks associated with hormone replacement therapy (HRT) for vasomotor symptoms in perimenopausal and postmenopausal women, alternative nonhormonal therapies are being investigated. In a randomized, double-blind, placebo-controlled study in 80 postmenopausal women who were experiencing more than 14 hot flushes weekly, 12 weeks of venlafaxine 75 mg daily was associated with a 51% reduction in hot flush score (patient's perception of hot flush interference with daily living). Although there also was a reduction in hot flush severity, the difference did not reach statistical significance. The role of venlafaxine therapy relative to other nonhormonal therapies (e.g., SSRIs, gabapentin) for postmenopausal vasomotor symptoms, both in terms of efficacy and safety, remains to be established.

Current evidence indicates that venlafaxine is well tolerated in the short-term treatment of vasomotor symptoms associated with breast cancer treatment and with menopause. The principal adverse effects associated with venlafaxine therapy in women with vasomotor symptoms have been dry mouth, decreased appetite, nausea, constipation, and difficulty sleeping. Additional study and experience are needed to further elucidate the role of venlafaxine relative to other nonhormonal therapies and to establish longer-term (i.e., beyond 4–12 weeks) efficacy and safety.

The possible role of venlafaxine in the management of vasomotor symptoms† associated with antiandrogenic therapy in men with prostate cancer remains to be determined.

■ **Obesity** Although substantial changes in appetite and weight have been reported in clinical studies of venlafaxine for the management of major depression, generalized anxiety disorder, social phobia, and panic disorder, the manufacturer states that the drug, alone or in combination with weight loss agents such as phentermine, is *not* indicated for the management of exogenous obesity†. Concomitant use of venlafaxine and weight loss agents also is not recommended by the manufacturer because the safety and efficacy of these agents when used concomitantly have not been established.

Dosage and Administration

■ **Administration** Venlafaxine hydrochloride is administered orally. To minimize GI intolerance (e.g., nausea), the manufacturer recommends that conventional venlafaxine tablets be taken with food. Food does not appear to affect GI absorption of the drug. Venlafaxine extended-release capsules should be administered as a single daily dose with food at approximately the same time each day (in the morning or evening). The extended-release capsules should be swallowed whole with fluid or the entire contents of a capsule(s) may be sprinkled on a small amount of applesauce immediately prior to administration. The extended-release capsules of venlafaxine and their contents should not be divided, crushed, chewed, or placed in water. If the capsule contents are administered by sprinkling on applesauce, the patient should drink some water

after swallowing the entire mixture without chewing to ensure that the pellets are completely swallowed.

Risk of Sustained Hypertension Venlafaxine therapy has been associated with sustained increases in blood pressure in some patients. An analysis of patients with sustained hypertension and patients whose hypertension resulted in discontinuance of the drug revealed that most blood pressure elevations were modest in severity (i.e., 10–15 or 8–28 mm Hg increases in supine diastolic blood pressure among patients receiving conventional or extended-release venlafaxine, respectively). However, sustained blood pressure increases of this magnitude could have adverse consequences in patients receiving the drug. In addition, some cases of elevated blood pressure requiring immediate treatment have been reported during postmarketing surveillance of the drug. Therefore, the manufacturer recommends that preexisting hypertension be controlled before initiating venlafaxine therapy and that regular blood pressure monitoring be performed in patients receiving the drug. In patients who experience a sustained increase in blood pressure during venlafaxine therapy, dosage reduction or discontinuance of the drug should be considered.

Risk of Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions Potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions have been reported with selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), including venlafaxine, and selective serotonin-reuptake inhibitors (SSRIs) alone, but particularly with concurrent use of other serotonergic drugs (including serotonin [5-hydroxytryptamine; 5-HT] type 1 receptor agonists ["triptans"], drugs that impair the metabolism of serotonin [e.g., monoamine oxidase inhibitors], or antipsychotics or other dopamine antagonists). Manifestations of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or GI symptoms (e.g., nausea, vomiting, diarrhea). In its most severe form, serotonin syndrome may resemble NMS, which is characterized by hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation in vital signs, and mental status changes. Patients receiving venlafaxine should be monitored for the development of serotonin syndrome or NMS-like signs and symptoms.

Serious (sometimes fatal) adverse reactions, possibly related to serotonin syndrome or NMS, have been reported in patients who received a monoamine oxidase (MAO) inhibitor shortly before or after venlafaxine therapy. Therefore, concomitant use of venlafaxine and MAO inhibitors is *contraindicated*. It is recommended that at least 2 weeks elapse between discontinuance of an MAO inhibitor and initiation of venlafaxine and that an interval of at least 1 week elapse between discontinuance of venlafaxine and initiation of an MAO inhibitor.

If concurrent therapy with venlafaxine and a 5-HT$_1$ receptor agonist (triptan) is clinically warranted, the patient should be observed carefully, particularly during initiation of therapy, when dosage is increased, or when another serotonergic agent is initiated. Concurrent use of venlafaxine and serotonin precursors (e.g., tryptophan) is not recommended.

If signs and symptoms of serotonin syndrome or NMS develop during venlafaxine therapy, treatment with venlafaxine and any concurrently administered serotonergic or antidopaminergic agents, including antipsychotic agents, should be discontinued immediately and supportive and symptomatic treatment should be initiated.

For additional information on serotonin syndrome, see Drug Interactions: Serotonergic Drugs, in Fluoxetine Hydrochloride 28:16.04.20.

Risk of Suicidality and Overdosage Worsening of depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior may occur in both adult and pediatric (see Administration: Pediatric Precautions, in Dosage and Administration) patients with major depressive disorder or other psychiatric disorders, whether or not they are taking antidepressants. This risk may persist until clinically important remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term, placebo-controlled studies of antidepressants (i.e., selective serotonin-reuptake inhibitors and other antidepressants) have shown an increased risk of suicidality in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. An increased suicidality risk was not demonstrated with antidepressants compared with placebo in adults older than 24 years of age and a reduced risk was observed in adults 65 years of age or older. It is currently unknown whether the suicidality risk extends to longer-term use (i.e., beyond several months); however, there is substantial evidence from placebo-controlled maintenance trials in adults with major depressive disorder that antidepressants can delay the recurrence of depression.

The US Food and Drug Administration (FDA) recommends that all patients being treated with antidepressants for any indication be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of therapy (i.e., the first few months) and during periods of dosage adjustments. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be advised to monitor patients on a daily basis for the emergence of agitation, irritability, or unusual changes in behavior, as well as the emergence of suicidality, and to report such symptoms immediately to a health-care provider.

Although a causal relationship between the emergence of symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and/or mania and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consequently, consideration should be given to changing the therapeutic regimen or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If a decision is made to discontinue therapy, venlafaxine dosage should be tapered as rapidly as is feasible but with recognition of the risks of abrupt discontinuance. (See Discontinuance of Therapy under Dosage and Administration: Dosage.)

The results of retrospective studies indicate that venlafaxine overdosage may be associated with an increased risk of fatal outcome compared with that observed with SSRIs but lower than that associated with tricyclic antidepressants. Epidemiologic studies have shown that venlafaxine-treated patients have a higher preexisting burden of suicide risk factors than patients treated with SSRIs. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in an overdosage as opposed to other characteristics of these venlafaxine-treated patients is not clear. As with other antidepressants, FDA and the manufacturer of venlafaxine recommend that the drug be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage.

Risk of Bipolar Disorder It is generally believed (though not established in controlled trials) that treating a major depressive episode with an antidepressant alone may increase the likelihood of precipitating a mixed or manic episode in patients at risk for bipolar disorder. Therefore, patients should be adequately screened for bipolar disorder prior to initiating treatment with an antidepressant; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, and depression). Venlafaxine is *not* approved for use in treating bipolar depression.

Risk of Mydriasis Mydriasis has been reported in association with venlafaxine therapy. Therefore, patients with elevated intraocular pressure or those at risk of angle-closure glaucoma should be monitored during treatment with the drug.

Pediatric Precautions Safety and efficacy of venlafaxine in children younger than 18 years of age have not been established.

Although clinical studies designed to primarily assess the effect of venlafaxine on the growth, development, and maturation of children and adolescents have not been conducted to date, the results from available studies suggest that the drug may adversely affect weight, height, and appetite. Should the decision be made to prescribe venlafaxine for unlabeled (off-label) uses in pediatric patients, the manufacturer recommends regular monitoring of height and weight during therapy, particularly during long-term administration of the drug. In addition, the manufacturer states that the long-term safety of therapy with venlafaxine extended-release capsules (beyond 6 months) has not been systematically evaluated to date. Because the results of clinical studies indicate that the occurrence of blood pressure elevations considered to be clinically important in children and adolescents was similar to that observed in adults receiving venlafaxine, the manufacturer advises that the precautions for adults also should apply to pediatric patients receiving the drug. (See Risk of Sustained Hypertension under Dosage and Administration: Administration.)

In placebo-controlled clinical studies in children and adolescents† 6–17 years of age, efficacy of venlafaxine (administered as extended-release capsules) was *not* established for major depressive disorder or generalized anxiety disorder, and there were increased reports of hostility and suicide-related adverse events such as suicidal ideation and self-harm. Hostility and suicidal ideation were the most common adverse effects leading to discontinuance of the drug in clinical studies in pediatric patients with major depressive disorder, each occurring in 2% of children and adolescents receiving venlafaxine extended-release capsules compared with less than 1 or 0% of those receiving placebo, respectively. In addition, abnormal/changed behavior was the most common adverse effect leading to discontinuance of the drug in clinical studies in pediatric patients with generalized anxiety disorder, occurring in 1% of children and adolescents receiving venlafaxine extended-release capsules compared with none of those receiving placebo. There were no suicides reported in any of these clinical studies.

FDA has determined that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. However, the FDA also states that depression and certain other psychiatric disorders are themselves associated with an increased risk of suicide. (See Cautions: Pediatric Precautions, in Fluoxetine Hydrochloride 28:16.04.20.) Anyone considering the use of venlafaxine in a child or adolescent for any clinical use must therefore balance the potential risks with the clinical need. (See Risk of Suicidality and Overdosage under Dosage and Administration: Administration.)

■ **Dosage** Dosage of venlafaxine hydrochloride is expressed in terms of venlafaxine.

Although no overall differences in efficacy or safety were observed between

geriatric and younger adults receiving venlafaxine, the possibility that some older patients may exhibit increased sensitivity to the drug cannot be ruled out. No age-related differences in the pharmacokinetics of venlafaxine have been identified and dosage adjustments are not necessary for geriatric patients on the basis of age alone; however, as with any drug used for the treatment of depression, generalized anxiety disorder, social phobia, or panic disorder, caution should be used when treating geriatric patients and dosage should be increased cautiously. In addition, the greater frequency of decreased hepatic and renal function observed in the elderly should be considered. (See Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

Venlafaxine also should be used with caution in patients whose underlying medical condition might be compromised by increases in heart rate (e.g., patients with hyperthyroidism, heart failure, or recent myocardial infarction), particularly when the venlafaxine dosage exceeds 200 mg daily.

Patients should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Risk of Suicidality and Overdosage under Dosage and Administration: Administration.)

Major Depressive Disorder For the treatment of major depressive disorder in adults, the recommended initial dosage of venlafaxine is 75 mg daily administered in 2 or 3 divided doses as conventional tablets or as a single daily dose when using the extended-release capsules. According to the manufacturer, an initial dosage of 37.5 mg daily (as extended-release capsules) for the first 4–7 days (followed by an increase to 75 mg daily) may be considered for some patients. If no clinical improvement is apparent, the dosage may be increased by increments of up to 75 mg daily at intervals of not less than 4 days. If clinically necessary, dosage can be increased up to 225 mg daily in divided doses as conventional tablets or in a single daily dose when using the extended-release capsules. Although studies with venlafaxine conventional tablets in outpatient settings did not demonstrate additional benefit from dosages exceeding 225 mg daily in moderately depressed patients, patients with more severe depression responded to a mean dosage of 350 mg daily. Whether higher dosages of venlafaxine extended-release capsules are needed for more severely depressed patients is unknown; however, the manufacturer states that experience with dosages of venlafaxine extended-release capsules exceeding 225 mg daily is very limited. The manufacturer states that venlafaxine dosage should not exceed 375 mg daily (usually administered in 3 divided doses) as conventional tablets or 225 mg daily as extended-release capsules.

If desired, patients with depression who are undergoing treatment with a therapeutic dose of conventional tablets may be switched to the extended-release capsules at the nearest equivalent daily venlafaxine dose (e.g., change 37.5 mg twice daily administered as conventional tablets to a 75-mg extended-release capsule administered once daily).

Although the optimum duration of venlafaxine therapy has not been established, the manufacturer states that acute depressive episodes require several months or longer of sustained antidepressant therapy. Results of 2 relapse prevention trials indicate that the antidepressant efficacy of venlafaxine is maintained for up to 6 months in patients receiving 75–225 mg once daily as extended-release capsules and for up to 12 months in those receiving 100–200 mg daily in 2 divided doses as conventional tablets. In these studies, the same dosage of venlafaxine was used for both acute-phase and maintenance treatment. Based on these limited data, it is not known whether the dosage required to induce remission of depression would be comparable to that required to maintain euthymia. The usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

Generalized Anxiety Disorder For the management of generalized anxiety disorder in adults, the initial dosage of venlafaxine as extended-release capsules recommended for most patients is 75 mg once daily. In some patients, it may be desirable to initiate therapy with a dosage of 37.5 mg daily given for the first 4–7 days, followed by an increase to 75 mg daily. Although a dose-response relationship for effectiveness in generalized anxiety disorder was not clearly established in clinical studies, certain patients not responding to a venlafaxine dosage of 75 mg daily may benefit from a higher dosage. Dosage in these patients may be increased in increments of up to 75 mg daily at intervals of not less than 4 days up to a maximum dosage of 225 mg daily.

The optimum duration of venlafaxine therapy for the management of generalized anxiety disorder has not been established. Although the drug has been used for up to 6 months in controlled clinical studies, the usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

Social Phobia For the management of social phobia in adults, the recommended initial dosage of venlafaxine for most patients is 75 mg once daily as extended-release capsules. In some patients, it may be desirable to initiate therapy with a dosage of 37.5 mg daily given for the first 4–7 days, followed by an increase to 75 mg daily. Although a dose-response relationship for effectiveness in social phobia was not clearly established in clinical studies, certain patients not responding to a venlafaxine dosage of 75 mg daily may benefit from a higher dosage. Dosage in these patients may be increased in increments of up to 75 mg daily at intervals of not less than 4 days up to a maximum dosage of 225 mg daily.

The optimum duration of venlafaxine therapy for the management of social phobia has not been established. The efficacy of venlafaxine for long-term therapy (i.e., longer than 12 weeks) has not been demonstrated in controlled clinical studies to date. The usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

Panic Disorder For the management of panic disorder in adults, the recommended initial dosage of venlafaxine is 37.5 mg once daily as extended-release capsules for 7 days, followed by 75 mg once daily as extended-release capsules for another 7 days. In clinical trials, 37.5 mg once daily was given initially for 7 days, then 75 mg once daily for 7 days; thereafter, dosage was increased in increments of 75 mg once daily every 7 days if necessary up to a maximum dosage of 225 mg daily. Although a dose-response relationship for effectiveness in panic disorder was not clearly established in fixed-dose clinical studies, certain patients not responding to a venlafaxine dosage of 75 mg daily may benefit from a higher dosage. Dosage in these patients may be increased in increments of up to 75 mg daily at intervals of not less than 7 days up to a maximum dosage of approximately 225 mg daily.

The optimum duration of venlafaxine therapy for the management of panic disorder has not been established. The efficacy of venlafaxine for long-term therapy (i.e., longer than 12 weeks) in prolonging time to relapse in responding patients has been demonstrated in a controlled clinical trial. However, the usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

Vasomotor Symptoms Although the optimum dosage for the treatment of vasomotor symptoms† in women with breast cancer and in postmenopausal women remains to be established, some clinicians suggest that venlafaxine be initiated at a dosage of 37.5 mg once daily as extended-release capsules, increasing as necessary to 75 mg once daily. In one clinical study, 75 mg once daily as extended-release capsules appeared to be optimal. Further increases in dosage do not appear to provide substantially increased benefit but are potentially more toxic.

Discontinuance of Therapy Because withdrawal effects may occur, abrupt discontinuance of venlafaxine should be avoided. When venlafaxine therapy is discontinued, dosage should be tapered gradually and the patient carefully monitored to reduce the risk of withdrawal symptoms. If intolerable symptoms occur following dosage reduction or upon discontinuance of treatment, venlafaxine therapy may be reinstituted at the previously prescribed dosage until such symptoms abate. Clinicians may resume dosage reductions at that time but at a more gradual rate.

Withdrawal symptoms reported in clinical studies in adults receiving venlafaxine for major depression or generalized anxiety disorder include agitation, anorexia, anxiety, confusion, impaired coordination, diarrhea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, headaches, hypomania, insomnia, nausea, nervousness, nightmares, sensory disturbances (including shock-like electrical sensations), somnolence, sweating, tremor, vertigo, and vomiting. Abrupt discontinuance or dosage reduction of venlafaxine has been associated with the appearance of new symptoms, the frequency of which increased with increased dosage and longer duration of treatment.

In clinical studies, venlafaxine hydrochloride extended-release capsules were discontinued by reducing the daily dosage by 75 mg at intervals of 1 week; however, individualized tapering may be necessary.

■ **Dosage in Renal and Hepatic Impairment** Since clearance of venlafaxine is decreased and elimination half-life is increased in patients with renal impairment, the manufacturer states that dosage of the drug should be reduced by 25–50% in patients with mild-to-moderate renal impairment and by 50% in those undergoing hemodialysis and administration of the dose withheld until the dialysis period is complete (4 hours). Venlafaxine dosage also should be reduced by 50% in patients with moderate hepatic impairment. The manufacturer's labeling should be consulted for more detailed information on the dosage modifications in these patient populations.

■ **Treatment of Pregnant Women during the Third Trimester** Some neonates exposed to venlafaxine, other selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), or selective serotonin-reuptake inhibitors late in the third trimester of pregnancy have developed complications, which have sometimes been severe and required prolonged hospitalization, respiratory support, enteral nutrition, and other forms of supportive care in special care nurseries. (For additional information, see Cautions: Pregnancy, Fertility, and Lactation, in Fluoxetine Hydrochloride 28:16.04.20.) Therefore, the clinician should carefully consider the potential risks and benefits of treating a pregnant woman with venlafaxine during the third trimester of pregnancy. In addition, consideration should be given to cautiously tapering venlafaxine therapy in the third trimester prior to delivery if the drug is administered during pregnancy.

Description

Venlafaxine hydrochloride, a selective serotonin- and norepinephrine-reuptake inhibitor (SNRI), is a phenylethylamine-derivative antidepressant and anxiolytic agent. Venlafaxine differs structurally and pharmacologically from other commercially available antidepressants, including tricyclic and tetracyclic antidepressants, and also differs from other commercially available agents used to treat generalized anxiety disorder.

The exact mechanisms of antidepressant and anxiolytic actions of venlafaxine have not been fully elucidated but appear to be associated with the drug's potentiation of neurotransmitter activity in the CNS. Venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. In vitro studies have demonstrated that venlafaxine and ODV do not possess any significant affinity for muscarinic cholinergic, H_1-histaminergic, or α_1-adrenergic receptors.

SumMon® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the labeling be consulted for detailed information on the usual cautious, precautions, and contraindications.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Venlafaxine Hydrochloride

Oral		
Tablets	25 mg (of venlafaxine)*	Effexor® (scored), Wyeth Venlafaxine Hydrochloride Tablets
	37.5 mg (of venlafaxine)*	Effexor® (scored), Wyeth Venlafaxine Hydrochloride Tablets
	50 mg (of venlafaxine)*	Effexor® (scored), Wyeth Venlafaxine Hydrochloride Tablets
	75 mg (of venlafaxine)*	Effexor® (scored), Wyeth Venlafaxine Hydrochloride Tablets
	100 mg (of venlafaxine)*	Effexor® (scored), Wyeth Venlafaxine Hydrochloride Tablets
Capsules, extended-release	37.5 mg (of venlafaxine)	Effexor® XR, Wyeth
	75 mg (of venlafaxine)	Effexor® XR, Wyeth
	150 mg (of venlafaxine)	Effexor® XR, Wyeth

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name
†Use is not currently included in the labeling approved by the US Food and Drug Administration

SELECTIVE SEROTONIN-REUPTAKE INHIBITORS 28:16.04.20

Citalopram Hydrobromide

■ Citalopram hydrobromide, a selective serotonin-reuptake inhibitor (SSRI), is an antidepressant.

Uses

Citalopram hydrobromide is used in the treatment of major depressive disorder. In addition, citalopram has been used for the treatment of obsessive-compulsive disorder†, panic disorder†, social phobia† (social anxiety disorder), alcohol dependence†, premenstrual dysphoric disorder†, premature ejaculation†, eating disorders†, diabetic neuropathy†, and posttraumatic stress disorder†.

■ **Major Depressive Disorder** Citalopram hydrobromide is used in the treatment of major depressive disorder. A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks). According to DSM-IV criteria, a major depressive episode includes at least 5 of the following 9 symptoms (with at least one of the symptoms being either depressed mood or loss of interest or pleasure): depressed mood most of the day as indicated by subjective report (e.g., feels sad or empty) or observation made by others; markedly diminished interest or pleasure in all, or almost all, activities most of the day; significant weight loss (when not dieting) or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite; insomnia or hypersomnia; psychomotor agitation or retardation (observable by others, not merely subjective feelings of restlessness or being slowed down); fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach or guilt about being sick); diminished ability to think or concentrate or indecisiveness (either by subjective account or as observed by others); and recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide.

Treatment of major depressive disorder generally consists of an acute phase (to induce remission), a continuation phase (to preserve remission), and a maintenance phase (to prevent recurrence). Various interventions (e.g., psychotherapy, antidepressant drug therapy, electroconvulsive therapy [ECT]) are used alone or in combination to treat major depressive episodes. Treatment should be individualized, and the most appropriate strategy for a particular patient is determined by clinical factors such as severity of depression (e.g., mild, moderate, severe), presence or absence of certain psychiatric features (e.g., suicide risk, catatonia, psychotic or atypical features, alcohol or substance abuse or dependence, panic or other anxiety disorder, cognitive dysfunction, dysthymia, personality disorder, seasonal affective disorder), and concurrent illness (e.g., asthma, cardiac disease, dementia, seizure disorder, glaucoma, hypertension). Demographic and psychosocial factors as well as patient preference also are used to determine the most effective treatment strategy.

While use of psychotherapy alone may be considered as an initial treatment strategy for patients with mild to moderate major depressive disorder (based on patient preference and presence of clinical features such as psychosocial stressors), combined use of antidepressant drug therapy and psychotherapy may be useful for initial treatment of patients with moderate to severe major depressive disorder with psychosocial issues, interpersonal problems, or a comorbid axis II disorder. In addition, combined use of antidepressant drug therapy and psychotherapy may be beneficial in patients who have a history of poor compliance or only partial response to adequate trials of either antidepressant drug therapy or psychotherapy alone.

Antidepressant drug therapy can be used alone for initial treatment of patients with mild major depressive disorder (if preferred by the patient) and usually is indicated alone or in combination with psychotherapy for initial treatment of patients with moderate to severe major depressive disorder (unless ECT is planned). ECT is not generally used for initial treatment of uncomplicated major depression, but is recommended as first-line treatment for severe major depressive disorder when it is coupled with psychotic features, catatonic stupor, severe suicidality, food refusal leading to nutritional compromise, or other situations when a rapid antidepressant response is required. ECT also is recommended for patients who have previously shown a positive response to or a preference for this treatment modality and can be considered for patients with moderate or severe depression who have not responded to or cannot receive antidepressant drug therapy. In certain situations involving depressed patients unresponsive to adequate trials of several individual antidepressant agents, adjunctive therapy with another agent (e.g., buspirone, lithium) or concomitant use of a second antidepressant agent (e.g., bupropion) has been used; however, such combination therapy is associated with an increased risk of adverse reactions, may require dosage adjustments, and (if not contraindicated) should be undertaken only after careful consideration of the relative risks and benefits. (See Drug Interactions: Serotonergic Drugs, Tricyclic and Other Antidepressants under Drug Interactions: Drugs Undergoing Hepatic Metabolism or Affecting Hepatic Microsomal Enzymes, and Drug Interactions: Lithium.)

The efficacy of citalopram for the management of major depression has been established in short-term (4–6 weeks' duration), placebo-controlled studies in outpatients 18–66 years of age who met DSM-III or -III-R criteria for major depressive disorder. In a 6-week study in which patients received fixed citalopram dosages of 10, 20, 40, or 60 mg daily, the drug was effective at dosages of 40 and 60 mg daily as measured by the Hamilton Depression Rating Scale (HAM-D) Total Score, the HAM-D Depressed Mood Item (Item 1), the Montgomery Asberg Depression Rating Scale, and the Clinical Global Impression (CGI) Severity Scale. This study showed no clear antidepressant effect of the 10 or 20 mg daily dosages, and the 60 mg daily dosage was not more effective than the 40 mg daily dosage.

In a 4-week, placebo-controlled study in depressed adult patients, of whom 85% met criteria for melancholia, those who were treated with citalopram (at an initial dosage of 20 mg daily, titrated to the maximum tolerated dosage or to a maximum daily dosage of 80 mg) showed greater improvement than patients receiving placebo on the HAM-D Total Score, HAM-D Item 1, and the CGI Severity score. In 3 additional placebo-controlled depression trials, the difference in response to treatment between patients receiving citalopram and patients receiving placebo was not statistically significant, possibly due at least in part to a high spontaneous response rate, a high placebo response rate, small sample size, or, in the case of one study, too low a dosage.

In 2 placebo-controlled studies, depressed adult patients who had responded to an initial 6- to 8-week course of citalopram (fixed dosage of 20 or 40 mg daily in one study and flexible dosages ranging from 20–60 mg daily in the second study) were randomized to continue receiving citalopram or placebo for up to 6 months. In both of these studies, patients receiving citalopram experienced substantially lower relapse rates over the subsequent 6 months compared with those receiving placebo. In the fixed-dose study, the decreased rate of depression relapse was similar in patients receiving 20 or 40 mg daily of citalopram. An analysis of these data for possible age-, gender-, and race-related effects on treatment outcome did not suggest any difference in antidepressant efficacy based on the age, gender, and race of the patient. In a placebo-controlled trial, citalopram also was shown to help prevent recurrences of depression in patients with recurrent major depression receiving the drug for up to 6–18 months.

While the optimum duration of citalopram therapy has not been established, many experts state that acute depressive episodes require several months or longer of sustained antidepressant therapy. In addition, some clinicians recommend that long-term antidepressant therapy be considered in certain patients at risk for recurrence of depressive episodes (such as those with highly recurrent unipolar depression). In placebo-controlled studies, citalopram has been shown to be effective for the long-term (e.g., up to 18 months) management of depression. In addition, the drug has been used in some patients for longer periods (e.g., up to 28 months) without apparent loss of clinical effect or increased

Chemistry and Stability

■ **Chemistry** Caffeine, like theobromine and theophylline, is a xanthine derivative. Caffeine occurs naturally in tea and coffee, but is prepared synthetically for commercial drug use. Caffeine is present in amounts of about 100–150 mg/180 mL of brewed coffee; 60–80 mg/180 mL of instant coffee; 40–100 mg/180 mL of tea; and 17–55 mg/180 mL of cola beverage.

Caffeine occurs as a white powder or white, glistening needles that are usually matted together. The drug is odorless and has a bitter taste. Caffeine, which may contain one molecule of water or be anhydrous, is sparingly soluble in water and in alcohol. The hydrate effloresces in air.

Various synthetic mixtures of caffeine have been prepared to increase its solubility. The mixture of caffeine and sodium benzoate contains 45–52% anhydrous caffeine and occurs as a white powder with a slightly bitter taste. The mixture is freely soluble in water and soluble in alcohol. Caffeine and sodium benzoate injection has a pH of 6.5–8.5. Citrated caffeine is a white powder with a bitter taste, obtained by combining caffeine with citric acid. Citrated caffeine is freely soluble in water and soluble in alcohol and contains approximately 50% anhydrous caffeine. Commercially available caffeine citrate injection and oral solution have a pH of 4.7.

■ **Stability** Commercially available caffeine and sodium benzoate injection and caffeine citrate injection and oral solution should be stored at 15–30°C. The commercially available injections and oral solution should be inspected visually for particulate matter and discoloration prior to administration. Vials containing discolored solution or visible particulate matter should be discarded.

Based on compatibility studies, the commercially available caffeine citrate injection is chemically stable for 24 hours at room temperature when mixed with any of the following solutions: 5% dextrose injection; 50% dextrose injection; Intralipid® 20% emulsion; Aminosyn® 20% solution; dopamine hydrochloride injection (diluted to 0.6 mg/mL with 5% dextrose injection); calcium gluconate 10% injection; heparin sodium injection (diluted to 1 unit/mL with 5% dextrose injection); fentanyl citrate injection (diluted to 10 mcg/mL with 5% dextrose injection).

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Caffeine

Oral		
Tablets	100 mg*	**Caffeine Tablets**
	200 mg*	**Caffeine Tablets**
Tablets, film-coated	200 mg*	**Caffeine Film-coated Tablets**
		No Doz® Maximum Strength Caplets®, Novartis
		Vivarin®, GlaxoSmithKline

Caffeine also is commercially available in combination with analgesics, antacids, antihistamines, antipyretics, antitussives, belladonna alkaloids, diuretics, ergotamine tartrate, expectorants, nasal decongestants, skeletal muscle relaxants, sympathomimetics, and vitamins.

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Caffeine and Sodium Benzoate

Parenteral		
Injection	250 mg/mL (equivalent to caffeine anhydrous 125 mg/mL and sodium benzoate 125 mg/mL)*	**Caffeine and Sodium Benzoate Injection**

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Caffeine Citrate

Oral		
Solution	20 mg/mL (equivalent to 10 mg/mL caffeine anhydrous)*	**Cafcit®**, MeadJohnson
		Caffeine Citrate Oral Solution
Parenteral		
Injection	20 mg/mL (equivalent to 10 mg/mL caffeine anhydrous)*	**Cafcit®**, MeadJohnson
		Caffeine Citrate Injection
Powder†		

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name
†Use is not currently included in the labeling approved by the US Food and Drug Administration

Dexmethylphenidate Hydrochloride

■ Dexmethylphenidate hydrochloride, the *d-threo* enantiomer of racemic methylphenidate hydrochloride, is a CNS stimulant that has pharmacologic actions that are qualitatively similar to those of amphetamines.

Uses

Dexmethylphenidate hydrochloride is used alone or combined with behavioral treatment as an adjunct to psychological, educational, social, and other remedial measures in the treatment of attention deficit hyperactivity disorder (ADHD).

■ **Attention Deficit Hyperactivity Disorder** Dexmethylphenidate hydrochloride is used alone or combined with behavioral treatment as an adjunct to psychological, educational, social, and other remedial measures in the treatment of ADHD (hyperkinetic disorder, hyperkinetic syndrome of childhood, minimal brain dysfunction) in carefully selected children 6 years of age and older, adolescents, and adults.

Efficacy of dexmethylphenidate hydrochloride conventional tablets for this indication was established in 2 placebo-controlled clinical trials in patients 6–17 years of age who met DSM-IV criteria for ADHD. In the first controlled clinical trial, improvement in symptom scores from baseline to study end (4 weeks) was greater in children receiving dexmethylphenidate hydrochloride conventional tablets than in those receiving placebo. In the second trial, children who had responded to dexmethylphenidate hydrochloride as conventional tablets in a 6-week open-label trial were randomized to receive this formulation of the drug for an additional 2 weeks or to receive placebo. Treatment failure occurred in 63% of patients receiving placebo compared with 17% of those receiving dexmethylphenidate.

Efficacy of dexmethylphenidate hydrochloride extended-release tablets for this indication was established in clinical trials in children 6 years of age and older, adolescents, and adults who met DSM-IV criteria for ADHD. In a controlled clinical trial in pediatric patients 6–17 years of age, improvement in symptoms from baseline to study end (7 weeks) was greater in children receiving dexmethylphenidate hydrochloride extended-release capsules than in those receiving placebo. Because a limited number of adolescents were enrolled in the trial, data from the trial were insufficient to adequately assess efficacy of the extended-release capsules in adolescents; however, efficacy of dexmethylphenidate hydrochloride extended-release capsules in adolescents is supported by pharmacokinetic data and by evidence of the efficacy of conventional tablets of the drug in this population. In a controlled clinical trial in adults 18–60 years of age, improvement in signs and symptoms of ADHD from baseline to study end (5 weeks) was greater in adults receiving dexmethylphenidate hydrochloride extended-release capsules than in those receiving placebo.

For further information on the management of ADHD, see Uses: Attention Deficit Hyperactivity Disorder, in Methylphenidate Hydrochloride 28:20.92.

Dosage and Administration

■ **Administration** Dexmethylphenidate hydrochloride conventional tablets are administered orally twice daily without regard to meals; the manufacturer recommends that doses be administered at least 4 hours apart.

Dexmethylphenidate hydrochloride extended-release capsules are administered orally once daily in the morning, with or without food. The capsules should be swallowed intact and should *not* be crushed, chewed, or divided. Alternatively, the entire contents of the extended-release capsule(s) may be sprinkled onto a small amount (e.g., a spoonful) of applesauce immediately prior to administration. The entire sprinkle/applesauce mixture should be taken immediately and should not be stored for use at a later time.

■ **Dosage** The recommended initial dosage of dexmethylphenidate hydrochloride as conventional tablets, in patients 6 years of age and older who currently are not receiving racemic methylphenidate or are receiving stimulants other than methylphenidate is 2.5 mg twice daily. In patients 6 years of age and older who are being transferred from racemic methylphenidate to dexmethylphenidate therapy, the initial dexmethylphenidate hydrochloride dosage is one-half the current methylphenidate hydrochloride dosage. Dosage of dexmethylphenidate hydrochloride may be increased by 2.5–5 mg daily at weekly intervals, up to a maximum dosage of 20 mg daily.

The recommended initial dosage of dexmethylphenidate hydrochloride as extended-release capsules in patients who currently are not receiving dexmethylphenidate or racemic methylphenidate or who are receiving stimulants other than methylphenidate is 5 mg once daily for pediatric patients 6 years of age and older or 10 mg once daily for adults. Patients currently receiving dexmethylphenidate hydrochloride conventional tablets may be switched to the extended-release capsules at the same total daily dosage. In patients being transferred from racemic methylphenidate to dexmethylphenidate therapy, the initial dexmethylphenidate hydrochloride dosage is one-half the current methylphenidate hydrochloride dosage. Dosage of dexmethylphenidate hydrochloride may be increased by 5 mg daily in pediatric patients or by 10 mg daily in adults at weekly intervals, up to a maximum dosage of 20 mg daily.

Dosage of dexmethylphenidate must be carefully adjusted according to individual requirements and response. The patient should be observed for a sufficient duration at a given dosage to ensure that maximum benefit has been achieved before dosage adjustment is considered. If a beneficial effect is not

attained after appropriate dosage adjustment over a 1-month period, dexmethylphenidate therapy should be discontinued. If paradoxical aggravation of symptoms or other adverse effects occur during dexmethylphenidate therapy, dosage should be reduced or the drug discontinued if necessary.

The long-term efficacy (i.e., exceeding 6 weeks for conventional tablets or 7 weeks for extended-release capsules) has not been evaluated systematically in controlled studies; therefore, the long-term usefulness of the drug should be reevaluated periodically in patients receiving dexmethylphenidate for extended periods. In patients who have responded to dexmethylphenidate therapy, the drug should be discontinued periodically to assess the patient's condition; improvement may be maintained temporarily or permanently after the drug is discontinued. For children or adolescents whose symptoms are not severe outside the school setting, drug holidays may be attempted for all or part of the summer to assess continuing efficacy and need for such therapy as well as to minimize adverse effects.

■ **Special Populations** No special population dosage recommendations at this time.

Cautions

■ **Contraindications** Marked anxiety, tension, and agitation, since dexmethylphenidate may aggravate these symptoms. Glaucoma. Motor tics or a family history or a diagnosis of Tourette's syndrome; however, the American Academy of Pediatrics (AAP) states that the presence of tics before or during medical management of ADHD is *not* an absolute contraindication to stimulant drug use. (See the opening discussion in Cautions, in Methylphenidate Hydrochloride 28:20.92.) Recent (within 14 days) administration of monoamine oxidase (MAO) inhibitors, since hypertensive crisis could result.

Known hypersensitivity to dexmethylphenidate, methylphenidate, or any ingredient in the formulation.

■ **Warnings/Precautions** ***Warnings*** Dexmethylphenidate hydrochloride shares the toxic potentials of racemic methylphenidate, and the usual precautions of racemic methylphenidate therapy should be observed.

Abuse Potential. Tolerance and psychologic dependence with varying degrees of abnormal behavior can occur with chronic abuse of dexmethylphenidate. Psychotic episodes can occur, particularly with parenteral abuse. Dexmethylphenidate should be used with caution in patients with a history of drug or alcohol dependence. Caution also may be indicated in patients with comorbid conduct disorder or a chaotic family. If the risk of drug abuse by the patient or the patient's peers or family is considered high, a nonstimulant drug may be preferable.

Withdrawal. Abrupt withdrawal of dexmethylphenidate following prolonged administration may unmask severe depression. Long-term follow-up may be required.

Sudden Death and Serious Cardiovascular Events. Although a causal relationship to stimulants has not been established, sudden unexplained death, stroke, and myocardial infarction have been reported in adults receiving usual dosages of stimulants for the treatment of ADHD. Sudden unexplained death also has been reported in children and adolescents with structural cardiac abnormalities or other serious cardiac conditions receiving usual dosages of CNS stimulants. Results of one retrospective, case-control epidemiologic study showed a possible association between use of stimulant medications (e.g., methylphenidate) and sudden unexplained death in healthy children and adolescents. (See Pediatric Use under Warnings/Precautions: Specific Populations, in Cautions.) Given the study limitations, the US Food and Drug Administration (FDA) is unable to conclude that these data affect the overall risk and benefit profile of stimulant medications used to treat ADHD in children and adolescents. Amphetamines or other stimulants should not be discontinued by parents of children or patients receiving these medications for ADHD before consulting with their clinician. Because of postmarketing reports and results of this and other epidemiologic studies, the FDA is conducting an ongoing review of safety of amphetamines and other stimulants to evaluate a possible link between use of these agents and sudden death in children. To determine whether there is a direct causal relationship between use of stimulants and serious adverse cardiovascular events, the Agency for Healthcare Research and Quality (AHRQ) and FDA announced in 2007 that they are collaborating on a large study evaluating clinical data on approximately 500,000 adults and children who received these drugs for management of ADHD during a 7-year period ending in 2005; data collection for the study is expected to be completed in 2009.

Children, adolescents, and adults who are being considered for stimulant therapy should undergo a thorough medical history review (including evaluation for a family history of sudden death or ventricular arrhythmia) and physical examination to detect the presence of cardiac disease, and should receive further cardiac evaluation (e.g., ECG, echocardiogram) if initial findings suggest such disease. Although some serious cardiac conditions are independently associated with an increased risk of sudden death, CNS stimulants generally should *not* be used in children, adolescents, or adults with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac conditions. Patients who develop exertional chest pain, unexplained syncope, or other manifestations suggestive of cardiac disease during stimulant therapy should undergo prompt cardiac evaluation.

For further information on screening for cardiac conditions, selecting appropriate candidates for stimulant therapy, and monitoring for treatment-emergent cardiac conditions, see Cardiovascular Precautions under Cautions: Precautions and Contraindications, in the Amphetamines General Statement 28:20.04.

Effects on Blood Pressure and Heart Rate. Stimulants cause modest increases in average blood pressure (i.e., by about 2–4 mm Hg) and heart rate (i.e., by about 3–6 beats/minute); larger increases may occur in some patients. Although modest increases would not be expected to have short-term sequelae, all patients should be monitored for larger changes in blood pressure and heart rate. Caution is advised in patients with underlying medical conditions that might be affected by increases in blood pressure or heart rate (e.g., hypertension, heart failure, recent myocardial infarction, ventricular arrhythmia).

Psychiatric Effects. Stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder.

Stimulants should be used with caution in the management of ADHD in patients with comorbid bipolar disorder because of the potential for precipitation of mixed or manic episodes in such patients. Prior to initiating stimulant therapy, patients with ADHD and comorbid depressive symptoms should be carefully screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, or depression).

Psychotic or manic symptoms (e.g., hallucinations, delusional thinking, mania) have been reported in children and adolescents without prior history of psychotic illness or mania who received usual dosages of stimulants. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% of patients receiving usual dosages of stimulants (i.e., methylphenidate, amphetamine) compared with 0% of those receiving placebo. If psychotic or manic symptoms occur during stimulant therapy, a causal relationship to stimulants should be considered, and discontinuance of therapy may be appropriate.

Aggressive behavior and hostility frequently are observed in children and adolescents with ADHD and have been reported in patients receiving drug therapy for the disorder. Although a causal relationship to stimulants has not been established, patients beginning treatment for ADHD should be monitored for the onset or worsening of aggressive behavior or hostility.

Growth Suppression. Prolonged administration of stimulants in children with ADHD has been associated with at least a temporary suppression of normal weight and/or height patterns in some patients. Results of an analysis of weight and height patterns in children 7–13 years of age suggested that treatment with methylphenidate for up to 3 years was associated with a temporary slowing in growth rate (on average, height gain was suppressed by about 2 cm and weight gain was suppressed by 2.7 kg over 3 years), without evidence of growth rebound during this period of development. In a 7-week controlled study in children and adolescents, patients receiving placebo gained a mean of 0.4 kg, while those receiving dexmethylphenidate hydrochloride extended-release capsules *lost* a mean of 0.5 kg. Published data are inadequate to determine whether long-term use of amphetamines may cause similar suppression of growth; however, it is anticipated that amphetamines, like methylphenidate, also cause temporary growth suppression. Therefore, the manufacturers of stimulant preparations state that growth should be monitored during therapy with stimulants, and children who are not growing or gaining height or weight as expected may require temporary discontinuance of therapy. However, AAP states that studies of stimulants in children generally have found little or no decrease in expected height, with any decrease in growth early in treatment being compensated for later on. (See Cautions: GI and Growth Effects, in Methylphenidate Hydrochloride 28:20.92.)

Seizures. There is some clinical evidence that stimulants may lower the seizure threshold in patients with a history of seizures, in those with prior EEG abnormalities but no history of seizures, and, very rarely, in those without a history of seizures and no prior evidence of EEG abnormalities. One patient, without a history of seizure disorder, experienced a seizure while receiving dexmethylphenidate during a controlled clinical trial. If seizures occur, the drug should be discontinued.

Visual Effects. Visual disturbances (difficulty with accommodation, blurred vision) have been reported in patients receiving stimulants.

General Precautions **Hematologic Monitoring.** The manufacturer recommends periodic monitoring of complete blood cell count (CBC), with differential, and platelet counts during prolonged therapy; however, AAP and many clinicians consider routine hematologic monitoring unnecessary in patients receiving recommended stimulants (e.g., methylphenidate, amphetamines) in the absence of clinical signs (e.g., fever, sore throat, unusual bleeding or bruising) suggestive of hematologic toxicity.

Specific Populations **Pregnancy.** Category C. (See Users Guide.)

Lactation. Not known whether dexmethylphenidate is distributed into milk; caution if used in nursing women.

Pediatric Use. Safety and efficacy of dexmethylphenidate not established in children younger than 6 years of age, and therefore the manufacturer states that the drug should not be used in this age group.

Therapy with stimulants may be associated with at least a temporary suppression of growth in children. (See Growth Suppression under Warnings/Precautions: Warnings, in Cautions.)

Sudden death has been reported in children and adolescents with structural cardiac abnormalities or other serious cardiac conditions receiving usual dosages of CNS stimulants. Results of one retrospective, case-control epidemio-

logic study suggested a possible association between use of stimulant medications and sudden unexplained death in healthy children and adolescents. (See Sudden Death and Serious Cardiovascular Events under Warnings/Precautions: Warnings, in Cautions.)

Renal Impairment. Safety and efficacy of dexmethylphenidate not established in patients with renal impairment.

Hepatic Impairment. Safety and efficacy of dexmethylphenidate not established in patients with hepatic impairment.

■ **Common Adverse Effects** Abdominal pain, fever, anorexia, and nausea each occurred in 5% or more of patients receiving dexmethylphenidate hydrochloride conventional tablets in clinical trials and were at least twice as frequent in patients receiving the drug as in those receiving placebo. Twitching (motor or vocal tics), anorexia, insomnia, and tachycardia each resulted in discontinuance of dexmethylphenidate hydrochloride conventional tablets in approximately 1% of patients.

Decreased appetite, headache, dyspepsia, dry mouth, anxiety, and pharyngolaryngeal pain each occurred in 5% or more of patients receiving dexmethylphenidate hydrochloride extended-release capsules in clinical trials. Twitching (motor or vocal tics), anorexia, insomnia, and tachycardia each resulted in discontinuance of dexmethylphenidate hydrochloride extended-release capsules in approximately 1% of pediatric patients. In adults, insomnia, jittery feeling, anorexia, and anxiety each resulted in discontinuance of therapy in about 1–2% of patients.

Nervousness and insomnia are the most commonly reported adverse effects in patients receiving racemic methylphenidate preparations.

Drug Interactions

The possibility that drug interactions reported with racemic methylphenidate also could occur with dexmethylphenidate should be considered.

■ **Cardiovascular Agents** Potential pharmacologic interaction (increased hypertensive effects) with concomitant use of pressor agents and dexmethylphenidate; caution advised. Pharmacodynamic interaction (decreased antihypertensive effect) reported with concomitant use of racemic methylphenidate and antihypertensive agents. Serious adverse effects have occurred rarely in patients receiving racemic methylphenidate and clonidine concomitantly; causality not established.

■ **Anticonvulsants** Potential pharmacokinetic interaction (decreased metabolism of anticonvulsant agent) with concomitant use of racemic methylphenidate and anticonvulsants (e.g., phenobarbital, phenytoin, primidone). Monitoring of plasma anticonvulsant concentrations is recommended when methylphenidate is initiated or discontinued in patients receiving anticonvulsants; adjustment of anticonvulsant dosage may be required.

■ **Anticoagulants** Potential pharmacokinetic interaction (decreased metabolism of anticoagulant) with concomitant use of racemic methylphenidate and coumarin anticoagulants. Monitoring of prothrombin time (PT)/international normalized ratio (INR) is recommended when methylphenidate is initiated or discontinued in patients receiving coumarin anticoagulants; adjustment of anticoagulant dosage may be required.

■ **Antidepressants** Pharmacologic interaction (possible hypertensive crisis) with monoamine oxidase (MAO) inhibitors. (See Cautions: Contraindications.) Pharmacokinetic interaction (decreased metabolism of antidepressant agent) reported with concomitant use of racemic methylphenidate and tricyclic antidepressants (e.g., imipramine, clomipramine, desipramine) or selective serotonin-reuptake inhibitors. Adjustment of antidepressant dosage may be required when methylphenidate is initiated or discontinued.

■ **Drugs Metabolized by Hepatic Microsomal Enzymes** Pharmacokinetic interaction unlikely.

■ **Drugs Affecting GI pH** Studies to evaluate the effects of changes in gastric pH on the absorption of dexmethylphenidate hydrochloride administered as extended-release capsules have not been performed to date. However, the potential exists for a pharmacokinetic interaction (altered release of dexmethylphenidate hydrochloride) between Focalin® XR extended-release capsules and drugs that alter gastric pH (e.g., antacids, acid suppressants).

Description

Dexmethylphenidate hydrochloride, the more pharmacologically active (*d-threo*) enantiomer of racemic methylphenidate hydrochloride, is a CNS stimulant. The mechanism of action in the treatment of attention deficit hyperactivity disorder (ADHD) has not been determined.

Dexmethylphenidate hydrochloride is well absorbed following oral administration. Because of first-pass metabolism, mean absolute bioavailability is 22–25%. When dexmethylphenidate hydrochloride is administered orally as conventional tablets in fasting patients, peak plasma concentrations are achieved within 60–90 minutes after a dose. When the drug is administered as extended-release capsules (Focalin® XR), peak plasma concentrations are attained at 1.5 hours and again at 6.5 hours after a dose. Extended-release capsules are absorbed more slowly but to the same extent as conventional tablets. Plasma concentrations of dexmethylphenidate achieved following single-dose oral administration of dexmethylphenidate hydrochloride capsules are comparable to the dexmethylphenidate concentrations achieved following single-dose oral administration of racemic methylphenidate hydrochloride capsules at equimolar doses (twice the total mg amount of dexmethylphenidate hydrochloride). Dexmethylphenidate is metabolized principally by de-esterification to form *d*-ritalinic acid, which has little or no pharmacologic activity. In vitro studies indicate that the drug does not inhibit the cytochrome P-450 (CYP) enzyme system. The mean plasma elimination half-life of dexmethylphenidate is 2–3 hours in children or 2–4.5 hours in adults.

Dexmethylphenidate hydrochloride is commercially available as conventional tablets and extended-release capsules. Each bead-filled dexmethylphenidate hydrochloride extended-release capsule (Focalin® XR) contains one-half of the dose as immediate-release beads and one-half as enteric-coated, delayed-release beads, thus providing an immediate release of dexmethylphenidate hydrochloride followed by a second delayed release of the drug.

Advice to Patients

Importance of providing patient or caregiver with a copy of the manufacturer's patient information (medication guide); discuss and answer questions about its contents (e.g., benefits and risks of stimulant therapy, appropriate use) as needed. Importance of instructing the patient or caregiver to read and understand the contents of the medication guide before initiating therapy and each time the prescription is refilled.

Importance of informing clinicians immediately of any adverse cardiovascular (e.g., chest pain, shortness of breath, fainting) or psychiatric effects (e.g., hallucinations, delusional thinking, mania).

Importance of taking the drug exactly as prescribed.

Importance of not chewing or crushing the beads contained in the capsules and of not storing the sprinkle/food mixture for later use.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs and herbal supplements, as well as any concomitant illnesses/conditions (e.g., glaucoma, cardiac/cardiovascular disease, mental/psychiatric disorder, seizures, suicidal ideation or behaviors, history of substance abuse).

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Dexmethylphenidate hydrochloride is subject to control under the Federal Controlled Substances Act of 1970 as a schedule II (C-II) drug.

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Dexmethylphenidate Hydrochloride

Oral		
Capsules, extended-release (containing beads)	5 mg (beads, delayed-release, enteric-coated extended-release 2.5 mg with immediate-release 2.5 mg)	**Focalin® XR** (C-II), Novartis
	10 mg (beads, delayed-release, enteric-coated extended-release 5 mg with immediate-release 5 mg)	**Focalin® XR** (C-II), Novartis
	15 mg (beads, delayed-release, enteric-coated extended-release 7.5 mg with immediate-release 7.5 mg)	**Focalin® XR** (C-II), Novartis
	20 mg (beads, delayed-release, enteric-coated extended-release 10 mg with immediate-release 10 mg)	**Focalin® XR** (C-II), Novartis
Tablets	2.5 mg	**Focalin®** (C-II), Novartis
	5 mg	**Focalin®** (C-II), Novartis
	10 mg	**Focalin®** (C-II), Novartis

mended human dosage on a mg/m² basis have not revealed evidence of fetal malformation. However, risperidone has been shown to cross the placenta in rats, and an increased rate of stillborn rat pups occurred at dosages 1.5 times higher than the maximum recommended human dosage on a mg/m² basis. In 3 reproductive studies in rats, there was an increase in pup deaths during the first 4 days of lactation at dosages 0.1–3 times the human dosage on a mg/m² basis. It is not known whether these deaths resulted from a direct effect on the fetuses or pups or to effects on the dams. In a separate reproductive study in rats, an increased number of pup daths (at birth or by the day after birth) and a decrease in birth weight were observed in pups of dams treated with risperidone dosages that were 3 times the maximum recommended human dosage on a mg/m² basis. Risperidone also appeared to impair maternal behavior, as evidenced by reduced weight gain and decreased survival (from day 1–4 of lactation) in pups born to control dams but reared by risperidone-treated dams.

Although there are no adequate and controlled studies to date in humans, one case of agenesis of the corpus callosum has been reported in an infant exposed to risperidone in utero; however, a causal relationship to risperidone therapy is unknown. Reversible extrapyramidal adverse effects in the neonate also were observed following postmarketing use of risperidone during the third trimester of pregnancy. Risperidone should be used during pregnancy only when the potential benefits justify the possible risks to the fetus. The effect of risperidone on labor and delivery in humans is unknown.

Risperidone (0.16–5 mg/kg) has been shown to impair mating, but not fertility, in Wistar rats in 3 reproductive studies at dosages 0.1–3 times the maximum recommended human dosage on a mg/m² basis. The effect appeared to be in females since impaired mating behavior was not noted in the Segment I study in which males only were treated. Sperm motility and serum testosterone concentrations were decreased in beagles at dosages 0.6–10 times the human dose on a mg/m² basis. Serum testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. A no-effect dosage was not found in these studies in either rats or dogs.

Risperidone and its principal active metabolite, 9-hydroxyrisperidone, are distributed into milk. The manufacturer states that women receiving risperidone should avoid nursing.

Description

Risperidone is a benzisoxazole-derivative antipsychotic agent and is chemically unrelated to other antipsychotic agents. While risperidone shares some of the pharmacologic actions of other antipsychotic agents, the drug has been described as an atypical or second-generation antipsychotic agent since many of its CNS effects differ from those of typical or first-generation agents (e.g., butyrophenones, phenothiazines). The exact mechanism of antipsychotic action of risperidone has not been fully elucidated but, like that of clozapine, appears to be more complex than that of most other antipsychotic agents and may involve antagonism of central type 2 serotonergic (5-HT_2) receptors and central dopamine D_2 receptors.

SumMon® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the labeling be consulted for detailed information on the usual cautions, precautions, and contraindications concerning potential drug interactions and/or laboratory test interferences and for information on acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Risperidone

Oral		
Solution	1 mg/mL	Risperdal®, Janssen
Tablets	0.25 mg	Risperdal® (scored), Janssen
	0.5 mg	Risperdal® (scored), Janssen
	1 mg	Risperdal® (scored), Janssen
	2 mg	Risperdal® (scored), Janssen
	3 mg	Risperdal® (scored), Janssen
	4 mg	Risperdal® (scored), Janssen
Tablets, orally disintegrating	0.5 mg	Risperdal® M-TAB®, Janssen
	1 mg	Risperdal® M-TAB®, Janssen
	2 mg	Risperdal® M-TAB®, Janssen
	3 mg	Risperdal® M-TAB®, Janssen
	4 mg	Risperdal® M-TAB®, Janssen
Parenteral		
For injectable suspension, extended-release, for IM use	25 mg	Risperdal® Consta® (available as dose pack containing a SmanSite® needle-free vial access device, a Needle-Pro® safety needle, and with 2-mL prefilled syringe diluent), Janssen
	37.5 mg	Risperdal® Consta® (available as dose pack containing a SmanSite® needle-free vial access device, a Needle-Pro® safety needle, and with 2-mL prefilled syringe diluent), Janssen
	50 mg	Risperdal® Consta® (available as dose pack containing a SmanSite® needle-free vial access device, a Needle-Pro® safety needle, and with 2-mL prefilled syringe diluent), Janssen

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Ziprasidone

■ Ziprasidone has been referred to as an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** ***Schizophrenia*** Ziprasidone is used for the symptomatic management of schizophrenia. Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Because of ziprasidone's greater capacity to prolong the QT/QT_c-interval compared with that of several other antipsychotic agents, use of ziprasidone may be reserved for patients whose disease fails to respond adequately to appropriate courses of other antipsychotic agents. (See Prolongation of QT interval under Warnings/Precautions: Warnings, in Cautions.) However, it should be noted that patients with a history of resistance to antipsychotic therapy (i.e., failed to respond to adequate courses of 2 or more antipsychotic agents) usually were excluded in clinical studies of ziprasidone.

Efficacy of oral ziprasidone was evaluated in 5 placebo-controlled studies of variable duration (4 short-term [4–6 weeks] and one long-term [52 weeks]), principally in patients with schizophrenic disorders in hospital settings. Ziprasidone appears to be superior to placebo in improving both positive and negative manifestations in acute exacerbations of schizophrenia and in reducing the rate of relapse for up to 52 weeks.

Although results of a limited comparative study suggest that oral ziprasidone hydrochloride dosages of 160 mg daily may be as effective as oral haloperidol 15 mg daily in reducing positive symptoms of schizophrenia, a reliable and valid comparison of ziprasidone and oral haloperidol cannot be made at this time based solely on this study due to its relatively small sample size (90 patients), high dropout rate (51.1%), and brief duration (4 weeks). Data from one unpublished comparative study also suggest that ziprasidone hydrochloride (mean dosage of 130 mg daily) may be as effective as olanzapine (mean dosage of 11 mg daily) in the treatment of schizophrenia.

Ziprasidone is used IM for the management of acute agitation in patients with schizophrenia for whom treatment with ziprasidone is appropriate and who require an IM antipsychotic agent for rapid control of behaviors that interfere with diagnosis and care (e.g., threatening behaviors, escalating or urgently distressing behavior, self-exhausting behavior). The efficacy of IM ziprasidone for the management of acute agitation in schizophrenia was established in single-day controlled trials in hospital settings. Because there is no experience regarding the safety of administering ziprasidone IM to schizophrenic patients already receiving oral ziprasidone, concomitant use of oral and IM formulations of ziprasidone is *not* recommended.

For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ **Bipolar Disorder** Ziprasidone is used for the treatment of acute manic and mixed episodes (with or without psychotic features) associated with bipolar I disorder. According to DSM-IV criteria, manic episodes are distinct periods lasting 1 week or longer (or less than 1 week if hospitalization is required) of abnormally and persistently elevated, expansive, or irritable mood accompanied by at least 3 (or 4 if the mood is only irritability) of the following 7 symptoms: grandiosity, reduced need for sleep, pressure of speech, flight of ideas, distractibility, increased goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation, and engaging in high risk behavior (e.g., unrestrained buying sprees, sexual indiscretions, foolish business investments).

Efficacy of ziprasidone in the treatment of acute manic and mixed episodes has been demonstrated in 2 short-term (3 weeks' duration), double-blind, pla-

cebo-controlled trials in patients who met the DSM-IV criteria for bipolar I disorder and who met diagnostic criteria for an acute manic or mixed episode (with or without psychotic features). The principal rating instruments used for assessing manic symptoms in these trials were the Mania Rating Scale (MRS), which is derived from the Schedule for Affective Disorders and Schizophrenia-Change Version (SADS-C) with items grouped as the Manic Syndrome subscale (e.g., elevated mood, less need for sleep, excessive energy, excessive activity, grandiosity), the Behavior and Ideation Subscale (irritability, motor hyperactivity, accelerated speech, racing thoughts, poor judgment), and impaired insight, and the Clinical Global Impression-Severity of Illness Scale (CGI-S), which was used to assess the clinical significance of treatment response.

In the first 3-week, placebo-controlled trial, ziprasidone hydrochloride was given at an initial dosage of 40 mg twice daily on the first day and 80 mg twice daily on the second day; dosage adjustment in 20-mg twice daily increments within a dosage range of 40–80 mg twice daily was then permitted for the remainder of the study. The mean daily dosage of ziprasidone hydrochloride in this study was 132 mg. In the second 3-week, placebo-controlled trial, patients also were given an initial dosage of ziprasidone hydrochloride 40 mg twice daily on the first day; subsequent dosage titration in 20-mg twice daily increments within a dosage range of 40–80 mg twice daily was permitted. The mean daily dosage of ziprasidone hydrochloride in this study was 112 mg daily. Ziprasidone was found to be superior to placebo in the reduction of the MRS total score and the CGI-S score in both of these studies.

For the initial management of less severe manic or mixed episodes in patients with bipolar disorder, current American Psychiatric Association (APA) recommendations state that monotherapy with lithium, valproate (e.g., valproate sodium, valproic acid, divalproex), or an antipsychotic such as olanzapine may be adequate. For more severe manic or mixed episodes, combination therapy with an antipsychotic and lithium or valproate is recommended as first-line therapy. For further information on the management of bipolar disorder, see Uses: Bipolar Disorder in Lithium Salts 28:28.

The manufacturer states that efficacy of ziprasidone has not been systematically evaluated for long-term use (i.e., exceeding 3 weeks) or for prophylactic use in patients with bipolar disorder.

Dosage and Administration

■ **Administration** Ziprasidone hydrochloride is administered orally twice daily with food. Ziprasidone mesylate is administered only by IM injection.

The commercially available lyophilized powder of ziprasidone mesylate for injection must be reconstituted prior to administration by adding 1.2 mL of sterile water for injection to single-dose vials of ziprasidone to provide a solution containing 20 mg/mL. Other solutions should not be used to reconstitute ziprasidone mesylate injection, and the drug should not be admixed with other drugs. The vials should then be shaken vigorously to ensure complete dissolution. Strict aseptic technique must be observed since the drug contains no preservative. Following reconstitution, ziprasidone mesylate for injection is stable for 24 hours when protected from light and stored at 15–30°C or for up to 7 days when refrigerated at 2–8°C. Ziprasidone mesylate injection should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

■ **Dosage** Dosage of ziprasidone hydrochloride is expressed in terms of the hydrochloride monohydrate. Dosage of ziprasidone mesylate is expressed in terms of ziprasidone.

Schizophrenia **Oral Dosage.** For the symptomatic management of schizophrenia, the recommended initial adult dosage of ziprasidone hydrochloride is 20 mg orally twice daily. Dosage may be increased after a minimum of 2 days at each dosage up to a maximum recommended dosage of 80 mg twice daily. To ensure use of the lowest effective dosage, however, it is recommended that patients be observed for several weeks prior to upward titrations of ziprasidone dosages. While a relationship between dosage and antipsychotic effect has not been established, the effective dosage of ziprasidone hydrochloride in clinical studies generally ranged from 20–100 mg twice daily. The manufacturer states that dosages exceeding 80 mg twice daily generally are not recommended, and safety of ziprasidone hydrochloride in dosages exceeding 100 mg twice daily has not been established.

The optimum duration of ziprasidone therapy currently is not known, but maintenance therapy with ziprasidone hydrochloride 20–80 mg twice daily has been shown to be effective for up to 52 weeks. However, the manufacturer states that no additional benefit has been demonstrated for ziprasidone hydrochloride dosages beyond 20 mg twice daily. Patients responding to ziprasidone therapy should continue to receive the drug as long as clinically necessary and tolerated, but at the lowest possible effective dosage, and the need for continued therapy with the drug should be reassessed periodically.

IM Dosage. For the prompt control of acute agitation in patients with schizophrenia, the recommended initial adult IM dose of ziprasidone is 10–20 mg given as a single dose. Depending on patient response, doses of 10 or 20 mg may be repeated every 2 or 4 hours, respectively, up to a maximum cumulative dose of 40 mg daily.

Oral therapy should replace IM therapy as soon as possible. Safety and efficacy of administering ziprasidone mesylate IM injection for longer than 3 consecutive days have not been evaluated. Because there is no experience regarding the safety of administering ziprasidone mesylate IM injection to patients with schizophrenia who already are receiving oral ziprasidone hydrochloride, the concomitant use of oral and IM formulations of ziprasidone is not recommended by the manufacturer.

Bipolar Disorder **Oral Dosage.** For the management of acute manic and mixed episodes associated with bipolar disorder (with or without psychotic features), the recommended initial adult dosage of ziprasidone hydrochloride is 40 mg orally twice daily on the first day of therapy. Dosage should then be increased to 60 or 80 mg twice daily on the second day of therapy. Subsequent dosage adjustments based on efficacy and tolerability may be made within a dosage range of 40–80 mg twice daily. In the flexible-dosage clinical trials, the mean daily dosage of ziprasidone hydrochloride was approximately 120 mg.

The optimum duration of ziprasidone hydrochloride therapy for bipolar disorder currently is not known. While it is generally agreed that pharmacologic treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of ziprasidone beyond 3 weeks. Therefore, the manufacturer states that clinicians who elect to use ziprasidone for extended periods should periodically reevaluate the long-term risks and benefits of the drug for the individual patient.

■ **Special Populations** No special population dosage recommendations at this time.

Cautions

■ **Contraindications** Known history of QT prolongation (including congenital long QT syndrome), recent acute myocardial infarction, or uncompensated heart failure. (See Prolongation of QT Interval under Warnings/Precautions: Warnings, in Cautions.) Concomitant therapy with other drugs that prolong the QT interval. (See Drug Interactions: Drugs that Prolong QT Interval.) Known hypersensitivity to ziprasidone.

■ **Warnings/Precautions** ***Warnings*** **Increased Mortality in Geriatric Patients with Dementia-related Psychosis.** Geriatric patients with dementia-related psychosis treated with atypical antipsychotic drugs appear to be at an increased risk of death compared with that among patients receiving placebo. Analyses of seventeen placebo-controlled trials (average duration of 10 weeks) revealed an approximate 1.6 - to 1.7-fold increase in mortality among geriatric patients receiving atypical antipsychotic drugs (i.e., aripiprazole, olanzapine, quetiapine, risperidone) compared with that in patients receiving placebo. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5% compared with a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. The manufacturer states that ziprasidone is not approved for the treatment of patients with dementia-related psychosis. (See Geriatric Use under Warnings/Precautions: Specific Populations, in Cautions.)

Prolongation of QT Interval. Prolongation of the QT interval can result in an occurrence of ventricular arrhythmias (e.g., torsades de pointes) and/or sudden death. In one study, oral ziprasidone prolonged the QT interval on ECG by a mean of 9–14 msec more than that observed in patients receiving risperidone, olanzapine, quetiapine, or haloperidol, but approximately 14 msec less than that observed in patients receiving thioridazine. In a study evaluating the QT/QT_c prolongation effect of IM ziprasidone, the mean increase in QT_c from baseline following 2 IM injections of ziprasidone (20 mg, then 30 mg, which is 50% higher than the recommended therapeutic dose) or haloperidol (7.5 mg, then 10 mg), given 4 hours apart, was 12.8 or 14.7 msec, respectively. Therefore, although torsades de pointes was not associated with ziprasidone therapy when the drug was administered at recommended dosages in premarketing clinical studies, experience with the drug is too limited to rule out the possibility that ziprasidone may be associated with a greater risk of sudden death than other antipsychotic agents. Patients at particular risk of torsades de pointes and/or sudden death include those with bradycardia, hypokalemia, or hypomagnesemia, those receiving concomitant therapy with other drugs that prolong the QT_c interval, and those with congenital prolongation of QT_c interval. The manufacturer states that ziprasidone should be avoided in patients with congenital prolongation of the QT interval or a history of cardiac arrhythmias and in those receiving concomitant therapy with other drugs that prolong the QT_c interval. (See Cautions: Contraindications and Drug Interactions: Drugs that Prolong QT Interval.)

Baseline serum potassium and magnesium concentrations should be determined in patients at risk for substantial electrolyte (i.e., potassium, magnesium) disturbances, particularly those receiving concomitant diuretic therapy, and hypokalemia or hypomagnesemia should be corrected prior to initiating ziprasidone. Clinical and ECG monitoring of cardiac function, including appropriate ambulatory ECG monitoring (e.g., Holter monitoring), is recommended during ziprasidone therapy in patients with symptoms that could indicate torsades de pointes (e.g., dizziness, palpitations, syncope). Ziprasidone therapy should be discontinued if the QT_c interval exceeds 500 msec.

Neuroleptic Malignant Syndrome. Although no cases have been confirmed to date in patients receiving ziprasidone, neuroleptic malignant syndrome (NMS), a potentially fatal syndrome requiring immediate discontinuance of the drug and intensive symptomatic treatment, may occur in patients receiving antipsychotic agents. For additional information on NMS, see Extrapyramidal Reactions under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Tardive Dyskinesia. Like other antipsychotic agents, use of ziprasidone may be associated with tardive dyskinesias, a syndrome of potentially irreversible, involuntary, dyskinetic movements. Although emergence of tardive dyskinesia was not specifically evaluated in clinical studies of ziprasidone, use of the drug was associated with either no change or small reductions in the Abnormal Involuntary Movement Scale (AIMS) scores from baseline in one year-long study of the drug. However, differences among antipsychotic agents in their potential to cause tardive dyskinesia have not been established definitively. For additional information on tardive dyskinesia, see Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Hyperglycemia and Diabetes Mellitus. Severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving certain atypical antipsychotic agents (e.g., clozapine, olanzapine, quetiapine, risperidone). While confounding factors such as an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population make it difficult to establish with certainty the relationship between use of agents in this drug class and glucose abnormalities, epidemiologic studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotic agents included in the studies (e.g., clozapine, olanzapine, quetiapine, risperidone); it remains to be determined whether ziprasidone also is associated with this increased risk. Although there have been few reports of hyperglycemia or diabetes in patients receiving ziprasidone, it is not known whether the paucity of such reports is due to relatively limited experience with the drug.

Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics currently are not available. While some evidence suggests that the risk for diabetes may be greater with some atypical antipsychotics (e.g., clozapine, olanzapine) than with others (e.g., quetiapine, risperidone) in the class, available data are conflicting and insufficient to provide reliable estimates of relative risk associated with use of the various atypical antipsychotics.

The manufacturers of atypical antipsychotic agents state that patients with preexisting diabetes mellitus in whom therapy with an atypical antipsychotic is initiated should be closely monitored for worsening of glucose control; those with risk factors for diabetes (e.g., obesity, family history of diabetes) should undergo fasting blood glucose testing upon therapy initiation and periodically throughout treatment. Any patient who develops manifestations of hyperglycemia during treatment with an atypical antipsychotic should undergo fasting blood glucose testing. In some cases, patients who developed hyperglycemia while receiving an atypical antipsychotic have required continuance of antidiabetic treatment despite discontinuance of the suspect drug; in other cases, hyperglycemia resolved with discontinuance of the antipsychotic.

For further information on managing the risk of hyperglycemia and diabetes mellitus associated with atypical antipsychotic agents, see Hyperglycemia and Diabetes Mellitus under Cautions: Precautions and Contraindications, in Clozapine 28:16.08.04.

Sensitivity Reactions **Rash.** Rash and/or urticaria, possibly related to dose and/or duration of therapy, occurred in about 5% of patients in clinical studies and have necessitated discontinuance of the drug in about 17% of these patients. Adjunctive treatment with antihistamines or steroids and/or drug discontinuance may be required. Discontinue ziprasidone if alternative etiology of rash cannot be identified.

General Precautions **Cardiovascular Effects.** Orthostatic hypotension, particularly during initial dosage titration period, has been reported. Use with caution in patients with known cardiovascular or cerebrovascular disease and/or conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia, concomitant antihypertensive therapy).

Nervous System Effects. Seizures occurred in about 0.4% of patients receiving ziprasidone in controlled clinical trials. Use with caution in patients with a history of seizures or with conditions known to lower the seizure threshold (e.g., Alzheimer's disease, geriatric patients).

Although not reported in clinical studies with ziprasidone, disruption of the body's ability to reduce core body temperature has been associated with use of other antipsychotic agents. Use caution when ziprasidone is administered in patients exposed to conditions that may contribute to an elevation in core body temperature (e.g., dehydration, extreme heat, strenuous exercise, concomitant use of anticholinergic agents).

GI Effects. Esophageal dysmotility and aspiration have been associated with the use of antipsychotic agents. Use with caution in patients at risk for aspiration pneumonia (e.g., geriatric patients, those with advanced Alzheimer's dementia). (See Increased Mortality in Geriatric Patients with Dementia-related Psychosis under Warnings/Precautions: Warnings, in Cautions and see Geriatric Use under Warnings/Precautions: Special Populations, in Cautions.)

Suicide. Attendant risk with psychotic illnesses; closely supervise high-risk patients. Prescribe in the smallest quantity consistent with good patient management to reduce the risk of overdosage.

Sexual Dysfunction. One case of drug-induced priapism reported in clinical studies of ziprasidone.

Other Metabolic and Endocrine Effects. Prolactin concentrations exceeding 22 ng/mL were reported in about 20% of patients receiving ziprasidone in phase II or III clinical studies compared with about 4, 46, or 89% of those receiving placebo, haloperidol, or risperidone, respectively.

Median weight gain of 0.5 kg occurred in patients receiving ziprasidone compared with no median weight change in those receiving placebo. In clinical studies, ziprasidone reportedly caused less weight gain than clozapine, olanzapine, quetiapine, or risperidone.

For additional information on metabolic effects, see Hyperglycemia and Diabetes Mellitus under Warnings/Precautions: Warnings, in Cautions.

Specific Populations **Pregnancy.** Category C. (See Users Guide.)

Lactation. Not known whether ziprasidone is distributed into milk; use in nursing women is not recommended.

Pediatric Use. Safety and efficacy not established in children younger than 18 years of age.

Geriatric Use. No substantial differences in safety of oral ziprasidone relative to younger adults have been observed in clinical studies. Ziprasidone mesylate IM injections have not been systematically evaluated in geriatric patients. Lower initial dosages, slower titration, and more careful monitoring during the initial dosing period may be advisable in some geriatric patients. (See Increased Mortality in Geriatric Patients with Dementia-related Psychosis under Warnings/Precautions: Warnings, in Cautions.)

Renal Impairment. Commercially available ziprasidone mesylate injections contain sulfobutylether β-cyclodextrin sodium, an excipient that is cleared by renal filtration. Therefore, ziprasidone injection should be used with caution in patients with renal impairment.

■ **Common Adverse Effects** Adverse effects occurring in more than 5% of patients with schizophrenia receiving oral ziprasidone and at least twice the frequency of placebo include somnolence (14%) and respiratory tract infection (8%).

Adverse effects occurring in more than 5% of patients with schizophrenia receiving IM ziprasidone 10 or 20 mg and at a frequency twice that reported among those receiving IM ziprasidone 2 mg include somnolence (20%), headache (13%), and nausea (12%).

Adverse effects occurring in more than 5% of patients with bipolar mania receiving oral ziprasidone and at least twice the frequency of placebo include somnolence (31%), extrapyramidal symptoms (31%), dizziness (16%), akathisia (10%), abnormal vision (6%), asthenia (6%), and vomiting (5%).

Drug Interactions

■ **Drugs that Prolong QT Interval** Potential pharmacologic interaction (additive effect on QT interval prolongation; concomitant use contraindicated) when ziprasidone is used with drugs that are known or consistently observed to prolong the QT_c interval (e.g., dofetilide, sotalol, quinidine, other Class Ia and III antiarrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate [no longer commercially available in the US], dolasetron mesylate, probucol, tacrolimus). Ziprasidone also is contraindicated in patients receiving drugs shown to cause QT prolongation as an effect and for which this effect is described in the full prescribing information as a contraindication or a boxed or bolded warning. (See Cautions: Contraindications and Prolongation of QT Interval under Warnings/Precautions: Warnings in Cautions.)

■ **Hypotensive Agents** Potential pharmacologic interaction (additive hypotensive effects).

■ **Other CNS Agents** Potential pharmacologic interaction (additive sedative effects).

■ **Levodopa and Dopamine Agonists** Potential pharmacologic interaction (antagonistic effects).

■ **Drugs Affecting Hepatic Microsomal Enzymes** Inhibitors or inducers of cytochrome P-450 (CYP) 3A4 isoenzyme; potential pharmacokinetic interaction (altered metabolism). Inhibitors or inducers of CYP1A2, CYP2C9, CYP2C19, or CYP2D6 isoenzymes: pharmacokinetic interaction unlikely.

■ **Protein-bound Drugs** Pharmacokinetic interaction unlikely.

Description

Ziprasidone is a benzisothiazolyl piperazine-derivative antipsychotic agent that is chemically unrelated to other currently available antipsychotic agents (e.g., butyrophenones, phenothiazines) and has been referred to as an atypical or second-generation antipsychotic agent. The exact mechanism of antipsychotic action of ziprasidone has not been fully elucidated but, like that of other atypical antipsychotic agents (e.g., olanzapine, risperidone), may involve antagonism of central type 2 serotonergic (5-HT_2) receptors and central dopamine D_2 receptors. As with other drugs that are effective in bipolar disorder, the precise mechanism of antimanic action of ziprasidone has not been fully elucidated. Antagonism of various other receptors (e.g., histamine H_1 receptors, α_1-adrenergic receptors) may contribute to other therapeutic and adverse effects (e.g., orthostatic hypotension, somnolence) observed with ziprasidone.

Ziprasidone is extensively metabolized in the liver principally via reduction by aldehyde oxidase with minimal excretion of unchanged drug in urine (less than 1%) or feces (less than 4%). About one-third of ziprasidone's metabolic clearance is mediated by the cytochrome P-450 (CYP) 3A4 isoenzyme. Ziprasidone did not inhibit CYP1A2, 2C9, 2C19, 2D6, or 3A4 isoenzymes in vitro.

Advice to Patients

Importance of reading manufacturer's patient information.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription (see Drug Interactions: Drugs That Prolong QT Interval) or OTC drugs, dietary supplements, and/or herbal products, as well as any concomitant illnesses (e.g., cardiovascular disease, diabetes mellitus).

Because somnolence and impairment of judgment, thinking, or motor skills may be associated with ziprasidone, avoid driving, operating machinery, or performing hazardous tasks while taking ziprasidone until gain experience with the drug's effects.

Importance of taking medication exactly as prescribed by the clinician.

Importance of women informing clinicians immediately if they are or plan to become pregnant or plan to breast-feed.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview (see Users Guide). For additional information until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Ziprasidone Hydrochloride

Oral		
Capsules	20 mg	Geodon®, Pfizer
	40 mg	Geodon®, Pfizer
	60 mg	Geodon®, Pfizer
	80 mg	Geodon®, Pfizer

Ziprasidone Mesylate

Parenteral		
For Injection, for IM use only	20 mg (of ziprasidone)	Geodon®, Pfizer

BUTYROPHENONES 28:16.08.08

Haloperidol

■ Haloperidol is a butyrophenone-derivative antipsychotic agent. The drug is considered a conventional or first-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** Haloperidol is used for the symptomatic management of psychotic disorders. Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to improve symptoms between episodes and to minimize the risk of recurrent acute episodes. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia and generally are effective in all subtypes of the disorder and subgroups of patients. Conventional antipsychotic agents, such as haloperidol, generally are considered to exhibit similar efficacy in treating acute psychotic symptoms, although they vary in their potency and adverse effect profile. Haloperidol is a high-potency antipsychotic that has been shown to be effective in the management of acute and stable phases of schizophrenia, but is frequently associated with extrapyramidal reactions such as akathisia, dystonia, or parkinsonian symptoms, even at low dosages.

Results of short-term studies indicate that haloperidol is more effective than placebo and equally or less effective than atypical antipsychotics in the treatment of positive (e.g., delusions, hallucinations) and negative symptoms (e.g., withdrawal from social interaction, blunted emotional expression) of schizophrenia. However, in one clinical study, haloperidol was less effective than the atypical antipsychotic agent risperidone in preventing relapse in adult outpatients with clinically active schizophrenia or schizoaffective disorders who were assigned to receive either drug for a minimum of 1 year. In this study, approximately 40% of patients in the study who received usual dosages of haloperidol had relapsed by the end of the study compared with approximately 25% of those receiving usual dosages of risperidone. Because atypical antipsychotics appear to be at least as effective in the treatment of positive symptoms and possibly more effective in the treatment of negative symptoms of schizophrenia and have fewer extrapyramidal reactions, some clinicians prefer use of atypical antipsychotics rather than conventional antipsychotics, such as haloperidol, for the management of schizophrenia, except in stable patients who have had good response to conventional antipsychotics without major adverse effects, in patients who require IM therapy, which is not yet available for some atypical antipsychotics, and for the acute management of aggression/violence in some patients, particularly those requiring long-acting (depot) parenteral preparations. However, patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

The long-acting decanoate ester of haloperidol is used parenterally principally in patients requiring prolonged antipsychotic therapy (e.g., patients with chronic schizophrenic disorder). Parenteral antipsychotic therapy with a long-acting preparation may be particularly useful in patients with a history of poor compliance. In addition, long-acting antipsychotic preparations may be useful in patients with suspected GI malabsorption or variable GI absorption of the drug. The principal disadvantage of long-acting parenteral antipsychotics is the inability to terminate the drug's action when severe adverse reactions occur. Long-acting antipsychotic preparations should not be used in the acute management of severely agitated patients. Generally, patients should be stabilized on antipsychotic medication prior to conversion to haloperidol decanoate therapy and should have previously received and tolerated a shorter-acting haloperidol preparation so that the possibility of an unexpected adverse reaction that potentially could not be readily reversed following the decanoate can be minimized. For further information on the use of antipsychotic agents in the symptomatic treatment of schizophrenia, see Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ **Tourette's Syndrome** Haloperidol is used for the control of tics and vocal utterances of Tourette's syndrome (Gilles de la Tourette's syndrome) in children and adults. Haloperidol generally has been considered the drug of choice for the management of Tourette's syndrome and pimozide has been be an effective alternative in some patients who have an inadequate response to or do not tolerate haloperidol. Because limited data suggest that pimozide may be more effective than haloperidol in reducing tics and pimozide appears to be better tolerated than haloperidol, some clinicians and experts prefer the use of pimozide in patients with Tourette's syndrome.

In children with tic disorders (e.g., Tourette's syndrome) and comorbid attention deficit hyperactivity disorder† (ADHD) in whom stimulants alone cannot control tics, haloperidol may be used concomitantly with a stimulant.

■ **Delirium** Antipsychotic agents, mainly haloperidol, have been used in the management of delirium†.

General Considerations Delirium is principally a disturbance of consciousness, attention, cognition, and perception but also may affect sleep, psychomotor activity, and emotions. It is a common psychiatric illness among medically compromised patients, particularly hospitalized patients, and may be a harbinger of substantial morbidity and mortality.

Prevalence and Course The prevalence of delirium in hospitalized medically ill patients ranges from 10–30%; in those who are elderly, delirium ranges up to 40%. Up to 25% of hospitalized cancer patients and 30–40% of hospitalized patients with acquired immunodeficiency syndrome (AIDS) develop delirium. Up to about 50% of postoperative patients develop delirium, and up to 80% of terminally ill patients develop it near death. EEG abnormalities, mainly generalized slowing, have fairly good sensitivity for aiding in the diagnosis of delirium, but the absence of such changes does not rule out the diagnosis. Prodromal manifestations may progress to full-blown delirium over 1–3 days; the duration of delirium generally ranges from less than a week to more than 2 months, but typically does not exceed 10–12 days. Symptoms persist for up to 30 days or longer in up to 15% of patients, and frequently persist for longer than 1 month in geriatric patients. Although most patients recover fully, delirium may progress to stupor, coma, seizures, and death, particularly if untreated. Full recovery is less likely in geriatric patients and patients with AIDS, possibly because of underlying dementia in both populations.

Underlying general medical conditions associated with delirium include CNS disorders (e.g., head trauma, seizures, postictal state, vascular or degenerative disease), metabolic disorders (e.g., renal or hepatic failure, anemia, hypoxia, hypoglycemia, thiamine deficiency, endocrinopathy, fluid or electrolyte imbalance, acid-base imbalance), cardiopulmonary disorder (myocardial infarction, congestive heart failure, cardiac arrhythmia, shock, respiratory failure), and systemic illness (e.g., substance intoxication or withdrawal, infection, cancer, severe trauma, sensory deprivation, temperature dysregulation, postoperative state).

Management Overview. Clinicians should undertake an essential array of psychiatric management tasks designed to provide immediate interventions for urgent general medical conditions, identify and treat the etiology of delirium, ensure safety of the patient and others in contact with the patient, and improve the patient's functioning. Environmental (e.g., varying light levels in intensive care units to heighten awareness about time of day and reduce the perception of timelessness) and supportive interventions (e.g., to deal with disorientation, to assure the patient that manifestations are temporary and reversible and do not reflect a persistent psychiatric disorder) also generally are offered to patients with delirium† and are designed to reduce factors that may exacerbate delirium, to reorient patients, and to provide support. Patients may have life-threatening medical conditions that require therapeutic intervention

even before a specific or definitive cause of the delirium is determined. The goal of diagnosis is to identify potentially reversible causes of delirium and prevent complications through prompt treatment of these specific disorders. Psychiatric management is essential and should be undertaken for all patients with delirium. Somatic interventions principally consist of drug therapy. The choice of somatic intervention will depend on the specific features of the patient's clinical condition, the underlying etiology of the delirium, and any associated comorbid conditions.

Drug Therapy. Antipsychotic agents often are the drugs of choice for the management of delirium†. Although other drugs (e.g., phenothiazines, droperidol) have been used, haloperidol generally is considered the antipsychotic of choice for most patients with delirium because of its relatively low risk of anticholinergic activity and of sedative and hypotensive effects. In addition, haloperidol has been studied most extensively, although few studies have used standardized definitions of delirium or reliable and valid delirium symptom rating measures to assess symptom severity before and after initiation of treatment. For drugs other than haloperidol, there have been no large, prospective studies that included a control. Evidence of efficacy for such alternative therapies, including second-generation antipsychotic agents (e.g., olanzapine, quetiapine, risperidone, ziprasidone), is principally from small case series, case reports, or open-label studies. In addition, interpretation of findings from many such case presentations is difficult because of use of nonstandardized delirium definitions and/or informal measures of delirium symptom severity. In general, evidence of the efficacy of antipsychotics, including haloperidol, in the management of delirium comes from numerous case reports and uncontrolled studies. However, evidence from a randomized, double-blind, comparator-drug controlled study (haloperidol, chlorpromazine, and lorazepam) in patients with AIDS that employed standardized clinical measures of delirium demonstrated clinical superiority of antipsychotic agents compared with benzodiazepines. Statistically significant improvement in the Delirium Rating Scale was evident after 2 days in patients receiving haloperidol or chlorpromazine but not in the lorazepam group (mean decreases in the score [i.e., improvement] were 8, 8.5, and 1, respectively). The symptomatic improvement in delirium occurred quickly among patients receiving antipsychotic therapy, usually before initiation of interventions directed at the medical etiologies of delirium.

Although various antipsychotic agents may be given orally, IM, or IV, IV administration is considered most effective in emergency situations or where oral access is limited. In addition, some evidence indicates that IV administration of antipsychotic agents may be associated with less severe extrapyramidal effects.

Special Precautions. Antipsychotic agents, particularly IV† haloperidol, used in the management of delirium have been associated with lengthening of the QT interval, possibly leading to atypical ventricular tachycardia (torsades de pointes), ventricular fibrillation, and sudden death. The manufacturer of Haldol® and the US Food and Drug Administration (FDA) state that although injectable haloperidol is approved *only* for IM injection and *not for IV administration*, there is considerable evidence from the medical literature that IV† administration of the drug is a relatively common, unlabeled ("off-label") clinical practice, principally for the treatment of severe agitation in intensive care units, and recommend ECG monitoring in any patient receiving the drug IV. Many clinicians also recommend that baseline and periodic or continuous ECG monitoring be performed with special attention paid to the length of the QT_c interval. Prolongation of the QT_c interval to greater than 450 msec or to greater than 15–25% over that in previous ECGs may warrant telemetry, a cardiology consultation, and dose reduction or discontinuance. Serum concentrations of magnesium and potassium also should be monitored at baseline and periodically in critically ill patients, especially those with baseline QT_c intervals of 440 msec or longer, those receiving other drugs known to increase the QT interval, and those who have electrolyte disorders. Limited evidence suggests that the incidence of torsades de pointes in patients receiving haloperidol IV is about 0.4–3.6%, but may increase to greater than 10% at relatively high IV doses (e.g., 35 mg or more over 24 hours). (See Cautions: Cardiovascular Effects and also see Cautions: Precautions and Contraindications.)

■ **Disruptive Behavior Disorder and Attention Deficit Hyperactivity Disorder** Haloperidol is used for the treatment of severe behavioral problems in children marked by combativeness and/or explosive hyperexcitable behavior (out of proportion to immediate provocations), and for the short-term treatment of hyperactive children who exhibit exeessive motor activity with accompanying conduct disorders that are manifested as impulsive behavior, difficulty sustaining attention, aggression, mood lability, and/or poor frustration tolerance. However, the possible risks of tardive dyskinesia, withdrawal dyskinesia, and other extrapyramidal reactions shonld be considered. Some experts currently reeommend use of haloperidol only for the treatment of comorbid tics in children with attention deficit hyperactivity disorder (ADHD). Some clinicians recommend routine administration of the Abnormal Involuntary Movement Scale (AIMS) to all children receiving antipsychotic agents.

■ **Nausea and Vomiting** Haloperidol also has been used in the prevention and control of severe nausea and vomiting† (e.g., cancer chemotherapy-induced emesis). Based on limited data, haloperidol appears to be as effective as phenothiazines in the prevention of cancer chemotherapy-induced emesis. Additional studies are required to determine the efficacy of haloperidol in the prevention and control of severe nausea and vomiting.

Dosage and Administration

■ **Administration** Haloperidol is administered orally. Haloperidol lactate is administered orally or by IM injection, and haloperidol decanoate is administered by IM injection. Pending accumulation of further data to establish safety and efficacy, IM administration of haloperidol lactate or decanoate in children is not recommended by the manufacturers. Haloperidol *lactate* also has been administered by IV injection† or infusion†. Haloperidol decanoate injection should *not* be administered IV.

Haloperidol decanoate should be administered by deep IM injection into the gluteal region using a 21-gauge needle. The manufacturers of haloperidol decanoate state that the maximum volume of haloperidol decanoate should not exceed 3 mL per IM injection site.

Haloperidol lactate and decanoate injections should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

■ **Dosage** Dosage of haloperidol lactate and the decanoate is expressed in terms of haloperidol.

There is considerable interindividual variation in optimum dosage requirements of haloperidol, and dosage must be carefully adjusted according to individual requirements and response, using the lowest possible effective dosage. Dosage should be increased more gradually in children and in debilitated, emaciated, or geriatric patients. Because of the risk of adverse reactions associated with cumulative effects of butyrophenones, patients with a history of long-term therapy with haloperidol and/or other antipsychotic agents should be evaluated periodically to determine whether maintenance dosage could be decreased or drug therapy discontinued.

Oral Dosage For the symptomatic management of psychotic disorders or Tourette's disorder in adults with moderate symptomatology and in geriatric or debilitated patients, the usual initial oral dosage of haloperidol is 0.5–2 mg 2 or 3 times daily. Subsequent dosage should be carefully adjusted according to the patient's tolerance and therapeutic response. Dosage during prolonged maintenance therapy should be kept at the lowest effective level.

The usual initial oral dosage of haloperidol for adults with severe symptomatology and/or chronic or resistant disorders is 3–5 mg 2 or 3 times daily. To achieve prompt control, higher dosages may be required in some patients. Patients who remain severely disturbed or inadequately controlled may require dosage adjustment. Oral dosages up to 100 mg daily may be required in some severely psychotic patients. Occasionally, dosages exceeding 100 mg daily have been used for the management of severely resistant disorders in adults; however, the safety of prolonged administration of such dosages has not been demonstrated.

The usual initial oral dosage of haloperidol in children 3–12 years of age and weighing 15–40 kg is 0.5 mg daily given in 2 or 3 divided doses. Subsequent dosage may be increased by 0.5 mg daily at 5- to 7-day intervals, depending on the patient's tolerance and therapeutic response.

For the symptomatic management of psychotic disorders in children 3–12 years of age, the usual oral dosage range is 0.05–0.15 mg/kg daily given in 2 or 3 divided doses; however, severely disturbed psychotic children may require higher dosages. Dosage during prolonged maintenance therapy should be kept at the lowest possible effective level; once an adequate response has been achieved, dosage should be gradually reduced and subsequently adjusted according to the patient's therapeutic response and tolerance.

For the management of non-psychotic behavioral problems and for the control of Tourette's disorder in children 3–12 years of age, the usual oral dosage range is 0.05–0.075 mg/kg daily given in 2 or 3 divided doses. Unlike psychotic disorders for which prolonged therapy is usually required, non-psychotic or hyperactive behavioral problems in children may be acute, and short-term administration of haloperidol may be adequate. A maximum effective dosage of haloperidol for the management of behavioral problems in children has not been established; however, the manufacturers state that there is little evidence that improvement in behavior is further enhanced at dosages greater than 6 mg daily.

IM Dosage For the prompt control of acutely agitated patients with moderately severe to very severe symptoms, the usual initial adult IM dose of haloperidol lactate is 2–5 mg (of haloperidol) given as a single dose. Depending on the response of the patient, this dose may be repeated as often as every hour; however, IM administration of haloperidol lactate every 4–8 hours may be adequate to control symptoms in some patients.

Oral therapy should replace short-acting parenteral therapy as soon as possible. Depending on the patient's clinical status, the first oral dose should be given within 12–24 hours following administration of the last parenteral dose of haloperidol lactate. Since bioavailability studies to establish bioequivalence between oral and parenteral dosage forms of haloperidol have not been conducted to date; the manufacturers suggest that the parenteral dosage administered during the preceding 24 hours be used for initial approximation of the total daily oral dosage required. Since this dosage is only an initial estimate, patients being switched from parenteral haloperidol lactate therapy to oral therapy should be closely monitored, particularly for clinical signs and symptoms of efficacy, sedation, and adverse effects, for the first several days following initiation of oral therapy. Subsequent dosage may be increased or decreased according to the patient's tolerance and therapeutic response, using the lowest possible effective dosage.

For patients requiring prolonged antipsychotic therapy (e.g., patients with